FILE 'REGISTRY' ENTERED AT 12:22:22 ON 08 APR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 6 APR 2004 HIGHEST RN 672263-62-6
DICTIONARY FILE UPDATES: 6 APR 2004 HIGHEST RN 672263-62-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when
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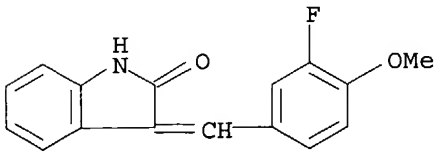
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can tot l3

L3 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN **384832-65-9** REGISTRY
CN 2H-Indol-2-one, 3-[(3-fluoro-4-methoxyphenyl)methylene]-1,3-dihydro- (9CI)
(CA INDEX NAME)
MF **C16 H12 F N O2**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

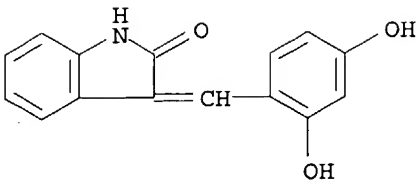
3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:207829

REFERENCE 2: 138:131086

REFERENCE 3: 136:64633

L3 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN **328106-29-2** REGISTRY
CN 2H-Indol-2-one, 3-[(2,4-dihydroxyphenyl)methylene]-1,3-dihydro- (9CI) (CA
INDEX NAME)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

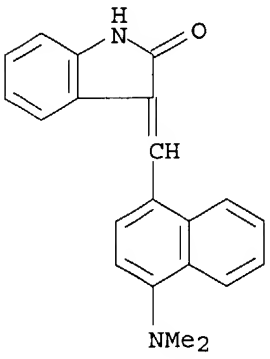
3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:207829

REFERENCE 2: 138:131086

REFERENCE 3: 136:64633

L3 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN **163655-37-6** REGISTRY
CN 2H-Indol-2-one, 3-[[4-(dimethylamino)-1-naphthalenyl]methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C21 H18 N2 O**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:207829

REFERENCE 2: 138:131086

REFERENCE 3: 136:64633

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                E MAE-87/CN
                E MAE87/CN

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L1              1 S US20030180294/PN OR WO2003-US05125/AP,PRN
                SEL RN

     FILE 'REGISTRY' ENTERED AT 12:15:14 ON 08 APR 2004
L2             10 S E1-E10
L3              3 S L2 AND (C15H11NO3 OR C16H12FNO2 OR C21H18N2O)
                E C15H11NO3/MF
L4             82 S E3 AND 46.150.18/RID AND NC4-C6/ES AND 3/NR
L5              4 S L4 AND DIHYDROXYPHENYL
L6              3 S L5 NOT ALDEHYDE
                E C16H12FNO2/MF
L7             47 S E3 AND 46.150.18/RID AND NC4-C6/ES AND 3/NR
L8             11 S L7 AND METHOXYPHENYL
L9              4 S L8 NOT ALDEHYDE
                E C21H18N2O/MF
L10            13 S E3 AND C6-C6/ES AND NC4-C6/ES AND 4/NR
L11             1 S L10 AND DIMETHYLAMINO
                SEL RN L3
L12             0 S E1-E3/CRN

     FILE 'HCAOLD' ENTERED AT 12:19:35 ON 08 APR 2004
L13             0 S L3

     FILE 'HCAPLUS' ENTERED AT 12:19:37 ON 08 APR 2004
L14             4 S L3
                E DEVRIES G/AU
L15             7 S E3,E8,E12,E13
                E DE VRIES G/AU
L16           105 S E3
L17            13 S E13
L18            12 S E23,E24
L19             1 S L14 AND L15-L18
L20             1 S L14 AND ALLERG?/PA,CS
L21             4 S L14,L19,L20
L22             0 S MAE87 OR MAE106 OR MAZ51 OR MAE()(87 OR 105) OR MAZ 51

     FILE 'USPATFULL, USPAT2' ENTERED AT 12:21:21 ON 08 APR 2004
L23             2 S L14
L24             1 S L22
L25             2 S L23,L24

     FILE 'BIOSIS' ENTERED AT 12:21:37 ON 08 APR 2004
L26             0 S L14 OR L22

     FILE 'EMBASE' ENTERED AT 12:21:40 ON 08 APR 2004
L27             0 S L14 OR L22

     FILE 'MEDLINE' ENTERED AT 12:21:52 ON 08 APR 2004
L28             0 S L14 OR L22
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FILE COVERS 1907 - 8 Apr 2004 VOL 140 ISS 15
FILE LAST UPDATED: 7 Apr 2004 (20040407/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L21 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:696673 HCAPLUS
DN 139:207829
ED Entered STN: 05 Sep 2003
TI Methods of extending corneal graft survival using VEGFR-3 inhibitors which inhibit lymphangiogenesis
IN **De Vries, Gerald W.**
PA **Allergan, Inc., USA**
SO PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 1-12 (Pharmacology)
Section cross-reference(s): 15
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003072029	A2	20030904	WO 2003-US5125	20030220
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003180294	A1	20030925	US 2002-81126	20020222
PRAI	US 2002-81126	A	20020222		

AB The present invention provides a method of extending corneal graft survival following corneal transplantation in a patient by administering

inhibitor, an ATP analog, a VEGFR-3 binding mol., or a sequence-specific RNase.

ST corneal graft survival VEGFR3 inhibitor lymphangiogenesis suppression

IT Protein motifs
(VEGFR-3 extracellular domain as inhibitor; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Enzyme functional sites
(active, inhibitor binds to the VEGFR-3 catalytic domain; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Angiogenesis inhibitors
Immunosuppressants
(addnl. therapeutic agent; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Antibodies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-VEGFR-3; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Antisense nucleic acids
Ribozymes
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as inhibitor; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Eye
(cornea, transplant; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Transplant and Transplantation
(cornea; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Nucleic acids
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(encoding VEGFR-3 dominant neg. receptor; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Lymphatic system
(lymph vessel, lymphangiogenesis; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Angiogenesis
(lymphangiogenesis; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Human
(methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Antibodies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal, anti-VEGFR-3; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Vascular endothelial growth factor receptors
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(type VEGFR-3, dominant neg. VEGFR-3 receptor; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT Vascular endothelial growth factor receptors

(inhibitor; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT 56-65-5D, 5'-ATP, analogs, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

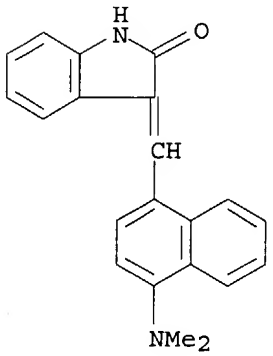
IT **163655-37-6P 328106-29-2P 384832-65-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of indolin-2-ones as VEGFR-3 inhibitors to increase corneal graft survival)

IT 59-48-3, Indolin-2-one 95-01-2, 2,4-Dihydroxy benzaldehyde 351-54-2, 3-Fluoro-4-methoxybenzaldehyde 1971-81-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of indolin-2-ones as VEGFR-3 inhibitors to increase corneal graft survival)

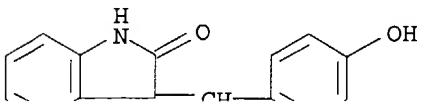
IT 9001-99-4, Ribonuclease
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sequence specific RNase as inhibitor; methods of extending corneal graft survival using VEGFR-3 inhibitors to inhibit lymphangiogenesis)

IT **163655-37-6P 328106-29-2P 384832-65-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of indolin-2-ones as VEGFR-3 inhibitors to increase corneal graft survival)

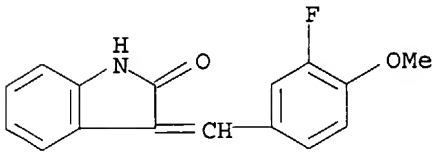
RN 163655-37-6 HCAPLUS
CN 2H-Indol-2-one, 3-[[4-(dimethylamino)-1-naphthalenyl]methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 328106-29-2 HCAPLUS
CN 2H-Indol-2-one, 3-[(2,4-dihydroxyphenyl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



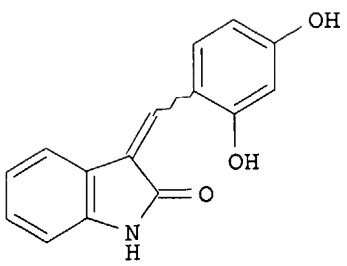
RN 384832-65-9 HCAPLUS
CN 2H-Indol-2-one, 3-[(3-fluoro-4-methoxyphenyl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



L21 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:76607 HCAPLUS
DN 138:131086
ED Entered STN: 31 Jan 2003
TI Indolin-2-one derivative protein kinase inhibitors, their preparation, and their therapeutic use
IN Chirchin, Vladimir; Athanassios, Giannis; Mazitschek, Ralph; Sleeman, Jonathan
PA Forschungszentrum Karlsruhe Gmbh, Germany
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM A61K031-404
ICS C07D209-34; A61P035-00
CC 1-6 (Pharmacology)
Section cross-reference(s): 27
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003007943	A1	20030130	WO 2002-EP7778	20020712
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	DE 10134196	A1	20030424	DE 2001-10134196	20010713
PRAI	DE 2001-10134196	A	20010713		

GI



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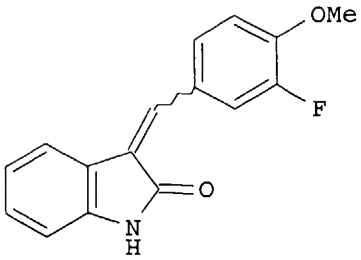

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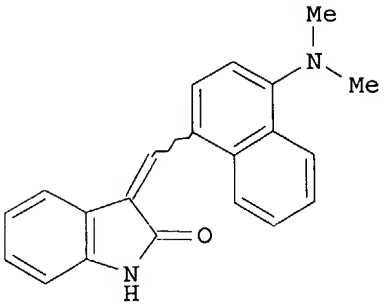


III

AB The invention discloses protein kinase inhibitors I, II, and III (preparation of these compds. is described) and the use thereof for treating diseases that are triggered by pathol. signal transduction cascades, e.g. cancer.

ST indolinone deriv prepn protein kinase inhibitor therapeutic; antitumor indolinone deriv protein kinase inhibitor; signal transduction disease therapeutic indolinone deriv protein kinase inhibitor

IT Animal cell line
(1AS; indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT Animal cell line
(HUVEC, endothelial cell proliferation; indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT Angiogenesis
(and lymphangiogenesis; indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT Phosphorylation, biological
(autophosphorylation; indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT Mammary gland, neoplasm
(carcinoma; indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT Blood vessel
(endothelium, endothelial cell proliferation; indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT Filaria
(filariasis; indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT Angiogenesis inhibitors
Antitumor agents
Apoptosis
Cell proliferation

(microvessel, endothelium, HDMEC cells, endothelial cell proliferation; indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT Phosphorylation, biological
(protein; indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT **163655-37-6P 328106-29-2P 384832-65-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT 59-48-3D, Indolin-2-one, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT 59-48-3 95-01-2, 2,4-Dihydroxybenzaldehyde 351-54-2, 3-Fluoro-4-methoxybenzaldehyde 1971-81-9, 4-Dimethylamino-1-naphthaldehyde
RL: RCT (Reactant); RACT (Reactant or reagent)
(indolinone derivative protein kinase inhibitor preparation and therapeutic use)

IT 79079-06-4, EGFR tyrosine kinase 103843-29-4, IGF1-R kinase 137632-09-8, ErbB2 receptor tyrosine kinase 144638-77-7, VEGFR-3 kinase 148047-29-4, TIE2 receptor kinase 150027-15-9, Gene FGFR1 tyrosine kinase 150977-45-0, VEGFR2 kinase 340830-03-7, Receptor tyrosine kinase 372092-80-3, Protein kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; indolinone derivative protein kinase inhibitor preparation and therapeutic use)

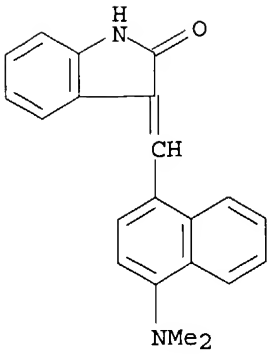
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Anon; WAHL; BAGARD: BULL SOC CHIM FR 1909, V4(5), P1038
(2) Bayer Ag; EP 0632102 A 1995 HCAPLUS
(3) Blum; BIOCHEMISTRY 2000, V39(51), P15705 HCAPLUS
(4) Hamada, K; BLOOD 2000, V12(96), P3793
(5) Kirkin, V; EUR J BIOCHEM 2001, V268, P5530 HCAPLUS
(6) McNutt, R; WO 9910325 A 1999 HCAPLUS
(7) Peter, H; WO 9807695 A 1998 HCAPLUS
(8) Sugen Inc; WO 9640116 A 1996 HCAPLUS

IT **163655-37-6P 328106-29-2P 384832-65-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(indolinone derivative protein kinase inhibitor preparation and therapeutic use)

RN 163655-37-6 HCAPLUS
CN 2H-Indol-2-one, 3-[[4-(dimethylamino)-1-naphthalenyl]methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 328106-29-2 HCAPLUS
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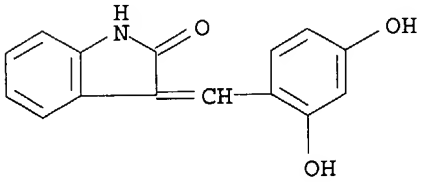
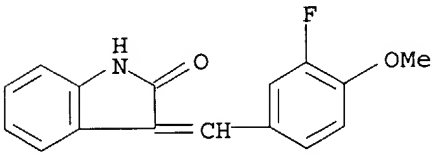


RN 384832-65-9 HCAPLUS
CN 2H-Indol-2-one, 3-[(3-fluoro-4-methoxyphenyl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



L21 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:811951 HCAPLUS
DN 136:64633
ED Entered STN: 08 Nov 2001
TI Characterization of indolinones which preferentially inhibit VEGF-C and VEGF-D-induced activation of VEGFR-3 rather than VEGFR-2
AU Kirkin, Vladimir; Mazitschek, Ralph; Krishnan, Jaya; Steffen, Anja; Waltenberger, Johannes; Pepper, Michael S.; Giannis, Athanassios; Sleeman, Jonathan P.
CS Forschungszentrum Karlsruhe, Institute of Genetics, Karlsruhe, D-76021, Germany
SO European Journal of Biochemistry (2001), 268(21), 5530-5540
CODEN: EJBCAI; ISSN: 0014-2956
PB Blackwell Science Ltd.
DT Journal

almost exclusively to lymphatic endothelium in the adult. Processed forms of VEGF-C and VEGF-D can also activate VEGFR-2, a key player in the regulation of angiogenesis. There is increasing evidence to show that these receptor-ligand interactions play a pivotal role in a number of pathol. situations. Inhibition of receptor activation by VEGF-C and VEGF-D could therefore be pharmaceutically useful. Furthermore, to understand the different roles of VEGF-C, VEGF-D, VEGFR-2 and VEGFR-3 in pathol. situations it will be necessary to dissect the complex interactions of these ligands and their receptors. To facilitate such studies we cloned, sequenced and characterized the expression of rat VEGF-C and VEGF-D. We showed that Cys152→Ser mutants of processed rat VEGF-C can activate VEGFR-3 but not VEGFR-2, while the corresponding mutation in rat VEGF-D inhibits its ability to activate both VEGFR-2 and VEGFR-3. We also synthesized and characterized indolinones that differentially block VEGF-C- and VEGF-D-induced VEGFR-3 kinase activity compared to that of VEGFR-2. These tools should be useful in analyzing the different activities and roles of VEGF-C, VEGF-D and their ligands, and in blocking VEGFR-3-mediated lymphangiogenesis.

ST indolinone prepn inhibitor VEGF C VEGF D receptor activation; rat VEGF C VEGF D cloning characterization

IT Phosphorylation, biological
Signal transduction, biological
(characterization of indolinones which preferentially inhibit VEGF-C and VEGF-D-induced activation of VEGFR-3 rather than VEGFR-2)

IT Protein sequences
Rat (Rattus norvegicus)
cDNA sequences
(cloning, sequencing and characterization of rat VEGF-C and VEGF-D)

IT Adrenal gland
Kidney
Lung
Mammary gland
Ovary
Spleen
Tongue
Tyson's gland
(cloning, sequencing, characterization, and tissue distribution of rat VEGF-C and VEGF-D)

IT Lymphatic system
(lymph vessel, endothelium; characterization of indolinones which preferentially inhibit the lymphangiogenic factors VEGF-C and VEGF-D-induced activation of VEGFR-3 rather than VEGFR-2)

IT Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type VEGFR-2; characterization of indolinones which preferentially inhibit VEGF-C and VEGF-D-induced activation of VEGFR-3 rather than VEGFR-2)

IT Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type VEGFR-3; characterization of indolinones which preferentially inhibit VEGF-C and VEGF-D-induced activation of VEGFR-3 rather than VEGFR-2)

IT 384965-73-5 384965-74-6
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; cloning, sequencing and characterization of rat VEGF-C and VEGF-D)

IT 144638-77-7, VEGFR-3 kinase 150977-45-0, VEGFR-2 kinase

(Biological study)
(characterization of indolinones which preferentially inhibit VEGF-C and VEGF-D-induced activation of VEGFR-3 rather than VEGFR-2)

IT **163655-37-6P 328106-29-2P 384832-65-9P**
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(characterization of indolinones which preferentially inhibit VEGF-C and VEGF-D-induced activation of VEGFR-3 rather than VEGFR-2)

IT 355108-88-2, GenBank AY032728 355108-89-3, GenBank AY032729
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; cloning, sequencing and characterization of rat VEGF-C and VEGF-D)

RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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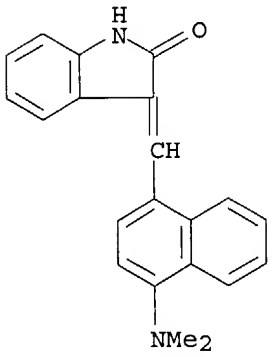
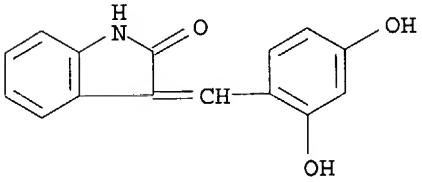
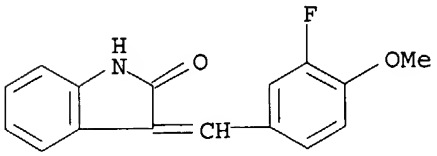
RN 163655-37-6 HCAPLUS
CN 2H-Indol-2-one, 3-[[4-(dimethylamino)-1-naphthalenyl]methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 328106-29-2 HCAPLUS
CN 2H-Indol-2-one, 3-[(2,4-dihydroxyphenyl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 384832-65-9 HCAPLUS
CN 2H-Indol-2-one, 3-[(3-fluoro-4-methoxyphenyl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



L21 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:599524 HCAPLUS
DN 122:316911
ED Entered STN: 09 Jun 1995
TI Dyes, their preparation, and bulk dyeing of plastics therewith.
IN Roschger, Peter
PA Bayer A.-G., Germany
SO Eur. Pat. Appl., 45 pp.
CODEN: EPXXDW
DT Patent

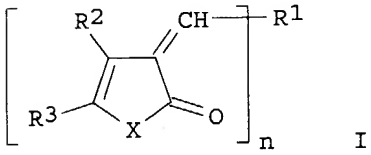
Section cross-reference(s): 38, 40

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 632102	A1	19950104	EP 1994-109171	19940615
	EP 632102	B1	19970402		
	R: CH, DE, FR, GB, LI				
	DE 4321420	A1	19950105	DE 1993-4321420	19930628
	DE 4340560	A1	19950601	DE 1993-4340560	19931129
	JP 07018586	A2	19950120	JP 1994-163334	19940623
	US 5626633	A	19970506	US 1995-566317	19951201
PRAI	DE 1993-4321420	A	19930628		
	DE 1993-4340560	A	19931129		
	US 1994-263222	B1	19940621		

OS MARPAT 122:316911

GI



I

AB The dyes I (n = 1, 2; R1 = aryl, heterocyclic group for n = 1 and direct bond or arylene for n = 2; R2, R3 = H, organic group: R2R3 = annellated ring; ; X = O, amino) are obtained from R1H or R1CH:Y (Y = O, amino compound) and the appropriate coreactant at 0-250°. Thus, 4-(dimethylamino)benzaldehyde was condensed with benzofuranone to give the dimethylaminobenzylidene derivative which could be used in the coloration of polystyrene.

ST dye plastic coloration

IT Polyamides, processes
Polycarbonates, processes
Polyesters, processes
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(dyes for bulk dyeing of plastics)

IT Dyes
(for bulk dyeing of plastics)

IT Dyeing
(bulk, of plastics)

IT 1090-41-1P 3051-47-6P 3051-50-1P 5812-07-7P 38711-15-8P
50793-69-6P 65155-71-7P 77811-51-9P 163655-03-6P 163655-04-7P
163655-05-8P 163655-06-9P 163655-07-0P 163655-08-1P 163655-09-2P
163655-10-5P 163655-11-6P 163655-12-7P 163655-13-8P 163655-14-9P
163655-15-0P 163655-16-1P 163655-17-2P 163655-18-3P 163655-19-4P
163655-20-7P 163655-21-8P 163655-22-9P 163655-23-0P 163655-24-1P
163655-25-2P 163655-26-3P 163655-27-4P 163655-28-5P 163655-29-6P
163655-30-9P 163655-31-0P 163655-32-1P 163655-33-2P 163655-34-3P
163655-35-4P 163655-36-5P **163655-37-6P** 163655-38-7P
163655-39-8P 163655-40-1P 163655-41-2P 163655-42-3P 163655-43-4P
163655-44-5P 163655-45-6P 163655-46-7P 163655-47-8P
RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); TEM (Technical or engineered material use); PREP (Preparation); PROC (Process); USES (Uses)

RL: PEP (Physical, engineering or chemical process); PROC (Process)
(dyes for bulk dyeing of plastics)

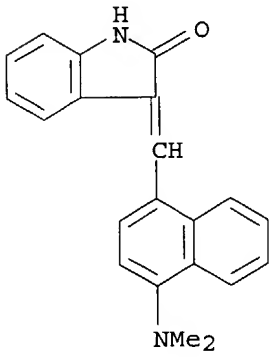
IT 163655-48-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; dyes for bulk dyeing of plastics)

IT 84-83-3 87-41-2, 1(3H)-Isobenzofuranone 100-10-7 123-11-5, 4-Methoxybenzaldehyde, reactions 591-12-8, α-Angelicalactone 2051-95-8, 3-Benzoylpropionic acid 4352-63-0, Naphtho[2,1-b]furan-2(1H)-one 4735-75-5 6050-80-2, Naphtho[1,2-b]furan-2(3H)-one 19828-45-6 31722-17-5 32438-34-9 80162-58-9 96838-79-8 103893-13-6 104094-17-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; dyes for bulk dyeing of plastics)

IT 59-48-3P 61-70-1P, 1-Methyl-2-indolone 92-14-8P, 4-(Diethylamino)-2-methylbenzaldehyde 623-27-8P, Terephthalaldehyde 1971-81-9P, 4-(Dimethylamino)-1-naphthalenecarboxaldehyde 3446-89-7P, 4-(Methylthio)benzaldehyde 14152-56-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(starting material; dyes for bulk dyeing of plastics)

IT **163655-37-6P**
RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); TEM (Technical or engineered material use); PREP (Preparation); PROC (Process); USES (Uses)
(dyes for bulk dyeing of plastics)

RN 163655-37-6 HCAPLUS
CN 2H-Indol-2-one, 3-[[4-(dimethylamino)-1-naphthalenyl]methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



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FILE 'USPATFULL' ENTERED AT 12:22:39 ON 08 APR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 12:22:39 ON 08 APR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

=> d bib abs kwic hitstr tot l25

L25 ANSWER 1 OF 2 USPATFULL on STN

DT Utility
FS APPLICATION
LREP CATHRYN CAMPBELL, CAMPBELL & FLORES LLP, 7th Floor, 4370 La Jolla Village Drive, San Diego, CA, 92122
CLMN Number of Claims: 38
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)
LN.CNT 2079
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a method of extending corneal graft survival following corneal transplantation in a patient by administering to the patient an effective amount of a pharmaceutical composition containing a vascular endothelial growth factor receptor-3 (VEGFR-3) inhibitor, whereby lymphangiogenesis is suppressed in the cornea of the patient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . block VEGF-C and VEGF-D induced VEGFR-3 kinase activity compared to that of VEGFR-2. Such specific VEGFR-3 kinase inhibitors, for example, **MAE106** and **MAZ51** can be prepared as described in Kirkin et al., Eur. J. Biochem. 268:5530-5540 (2001). Additional VEGFR-3 kinase inhibitors, including specific,. . .
DETD [0108] 3(2,4-dihydroxy-benzylidene)-1,3-dihydro-indol-2-one (**MAE87**), 3-(3-fluoro-4-methoxy-benzylidene)-1,3-dihydro-indol-2-one (**MAE106**) and 3-(4-dimethylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (**MAZ51**) were prepared essentially as follows. Indolin-2-one (10 mmol) is mixed with 10 mmol of either 2,4-dihydroxy-benzaldehyde (**MAE87**), 3-fluoro-4-methoxy-benzaldehyde (MAE 106) or 4-dimethylamino-naphthalene-1-carbaldehyde (**MAZ51**). The reactions are refluxed for 5 hours with three drops piperidine in 40 mL ethanol (Kirkin et al., supra, 2001).. . . filtered, washed with ethanol and dried under vacuum. The structures are shown below in Table 2. The melting point of **MAE87** is 250° C.; the melting point of **MAE106** is 220° C.; and the melting point of **MAZ51** is greater than 250° C.
TABLE 2

MAE87

##STR1##

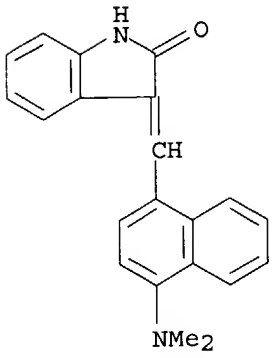
MAE106

##STR2##

MAZ51

##STR3##
DETD [0109] The VEGFR-3 tyrosine kinase inhibitor **MAE87**, **MAE106** or **MAZ51** is administered systemically at various concentrations, ranging from 0.5 to 200 mg/kg/day. In other animals, the compound is administered as. . .
DETD [0110] Animals receiving only vehicle demonstrate evidence of graft rejection, on average, at day 30. In contrast, in animals receiving **MAE87**, **MAE106** or **MAZ51** exhibit increased mean graft survival as demonstrated by a significant delay in evidence of graft rejection.

graft survival)
RN 163655-37-6 USPATFULL
CN 2H-Indol-2-one, 3-[[4-(dimethylamino)-1-naphthalenyl]methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 328106-29-2 USPATFULL
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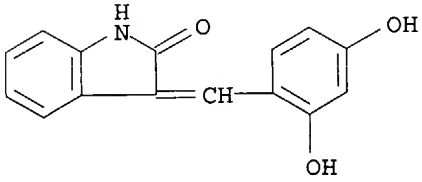
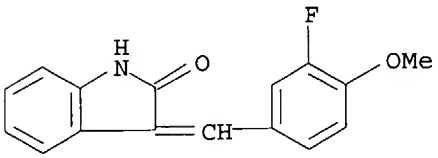


RN 384832-65-9 USPATFULL
CN 2H-Indol-2-one, 3-[(3-fluoro-4-methoxyphenyl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



L25 ANSWER 2 OF 2 USPATFULL on STN
AN 97:37980 USPATFULL
TI Bulk dyeing of plastics
IN Roschger, Peter, Koln, Germany, Federal Republic of
PA Bayer Aktiengesellschaft, Leverkusen, Germany, Federal Republic of (non-U.S. corporation)
PI US 5626633 19970506
AI US 1995-566317 19951201 (8)
RLI Continuation of Ser. No. US 1994-263222, filed on 21 Jun 1994, now

EXNAM Primary Examiner: Lieberman, Paul; Assistant Examiner: Dusheck, Caroline L.
LREP Sprung Horn Kramer & Woods
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 969
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Dyestuffs of the formula (I) ##STR1## wherein n denotes 1 or 2,

T denotes O or N--R.sub.0, wherein

R.sub.0 denotes H, alkyl, aryl or acyl or, together with R.sub.2 or R.sub.3, forms a 5- to 7-membered ring,

R.sub.1 if n=1, denotes aryl, hetaryl or heterocyclylidenemethyl and

if n=2, denotes a direct bond or arylene and

R.sub.2 and R.sub.3 are independent or cyclic radicals having the meanings given in the description,

are employed for bulk dyeing of plastics, preferably thermoplastics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 1090-41-1P 3051-47-6P 3051-50-1P 5812-07-7P 38711-15-8P
50793-69-6P 65155-71-7P 77811-51-9P 163655-03-6P 163655-04-7P
163655-05-8P 163655-06-9P 163655-07-0P 163655-08-1P 163655-09-2P
163655-10-5P 163655-11-6P 163655-12-7P 163655-13-8P 163655-14-9P
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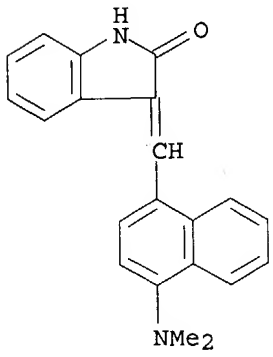
163655-44-5P 163655-45-6P 163655-46-7P 163655-47-8P
(dyes for bulk dyeing of plastics)
IT **163655-37-6P**
(dyes for bulk dyeing of plastics)
RN 163655-37-6 USPATFULL
CN 2H-Indol-2-one, 3-[[4-(dimethylamino)-1-naphthalenyl]methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



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NEWS 7	OCT 21	BIOSIS file reloaded and enhanced
NEWS 8	OCT 28	BIOSIS file segment of TOXCENTER reloaded and enhanced
NEWS 9	NOV 24	MSDS-CCOHS file reloaded
NEWS 10	DEC 08	CABA reloaded with left truncation
NEWS 11	DEC 08	IMS file names changed
NEWS 12	DEC 09	Experimental property data collected by CAS now available in REGISTRY
NEWS 13	DEC 09	STN Entry Date available for display in REGISTRY and CA/CAplus
NEWS 14	DEC 17	DGENE: Two new display fields added
NEWS 15	DEC 18	BIOTECHNO no longer updated
NEWS 16	DEC 19	CROPU no longer updated; subscriber discount no longer available
NEWS 17	DEC 22	Additional INPI reactions and pre-1907 documents added to CAS databases
NEWS 18	DEC 22	IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
NEWS 19	DEC 22	ABI-INFORM now available on STN
NEWS 20	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS 21	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
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NEWS 24	MAR 03	MEDLINE file segment of TOXCENTER reloaded
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NEWS 26	MAR 29	Pharmaceutical Substances (PS) now available on STN
NEWS 27	MAR 29	WPIFV now available on STN
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NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items

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	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

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FILE 'EMBASE' ENTERED AT 10:50:44 ON 08 APR 2004

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FILE 'SCISEARCH' ENTERED AT 10:50:44 ON 08 APR 2004

FILE 'CAPLUS' ENTERED AT 10:50:44 ON 08 APR 2004
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=> s corneal transplant
L1 1899 CORNEAL TRANSPLANT

=> s l1 and model
L2 206 L1 AND MODEL

=> s l2 and tyrosine kinase inhibitor
L3 0 L2 AND TYROSINE KINASE INHIBITOR

=> s l2 and VEGFR3
L4 0 L2 AND VEGFR3

=> s l2 and graft survival
L5 65 L2 AND GRAFT SURVIVAL

=> dup remove l5
PROCESSING COMPLETED FOR L5
L6 40 DUP REMOVE L5 (25 DUPLICATES REMOVED)

=> s l6 and "MAE87"
L7 0 L6 AND "MAE87"

=> s l5 and VEGF
L8 1 L5 AND VEGF

=> d l8 cbib abs

K.; Okuda T.. Dr. T. Okuda, [illegible]
Institute of Internal Medicine, University of Tsukuba, 1-1-1 Tennodai Tsukuba, Ibaraki 305, Japan. Transplantation 66/11 (1519-1524) 15 Dec 1998.
Refs: 18.
ISSN: 0041-1337. CODEN: TRPLAU. Pub. Country: United States. Language: English. Summary Language: English.

AB Background. Studies in **corneal transplant** rejection remain important because acute immunologic rejection continues to be the leading cause of human **corneal transplant** failure. As the permeability of vessels and the neovascularization induce cells infiltration into the graft, we considered the possibility that vascular endothelial growth factor (**VEGF**), a potent permeability-increasing factor and angiogenesis-mediating factor, could participate in the immune response. Methods. As the established **corneal transplant model** for rejection, the **corneal transplant** between Lewis and Fisher rats has been reported. First, we evaluated **VEGF** production in the graft by immunohistochemical method in the animal **model**. Next, we tried to neutralize the effect of **VEGF** by topical administration of anti-**VEGF** antibody. We administered anti-**VEGF** antibody as eye drops for 10 days just after the transplantation of the established animal **corneal transplant model**. Results. **VEGF** was strongly produced from the infiltrative cells into the graft. Anti-**VEGF** antibody significantly suppressed the acute rejection compared with saline or rabbit IgG. Conclusions. The inhibition of **VEGF** by topically applied neutralizing antibody is a new potential therapeutic strategy for the treatment of corneal transplantation.

=> d l6 1-40 cbib abs

L6 ANSWER 1 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2004104691 EMBASE Factors affecting rejection of second **corneal transplants** in rats. Banerjee S.; Dick A.D.; Nicholls S.M.. S. Banerjee, Division of Ophthalmology, School of Medical Sciences, University Walk, Bristol, BS8 1TD, United Kingdom. S.Banerjee@bris.ac.uk. Transplantation 77/4 (492-496) 27 Feb 2004.
Refs: 30.
ISSN: 0041-1337. CODEN: TRPLAU. Pub. Country: United States. Language: English. Summary Language: English.

AB Background. Second and subsequent **corneal transplants** in the same eye are more prone to rejection reactions and failure than first grafts. This may be a result of local changes or systemic sensitization to antigen shared by the first and second donors. Because HLA typing is not routine in corneal transplantation, a clear correlation between accelerated rejection and specific sensitization has not been established. Methods. PVG (RT1(c)), Lewis (LEW; RT1(1)), or AO (RT1(u)) strain corneas were transplanted to PVG strain rats, followed by a LEW strain cornea in the ipsilateral or contralateral eye 6 weeks later. **Graft survival** was evaluated by slit lamp biomicroscopy. Proliferation of recipient lymph node cells was tested against allogeneic, syngeneic and third-party stimulator cells after the second transplantation. Results. A second allograft in the ipsilateral or contralateral eye was rejected in an accelerated fashion that was not [illegible] accelerated in the

graft. Accelerated rejection [illegible]
the grafts. It could be caused by shared "public" MHC determinants, by minor antigens shared by the first and second donors, or by cross-reactivity of T cells to epitopes on AO and LEW grafts. HLA mismatching of first and second donors may not prolong second **graft survival**.

L6 ANSWER 2 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003488531 EMBASE Significant prolongation of orthotopic corneal-**graft survival** in FTY720-treated mice. Zhang E.-P.; Muller A.; Ignatius R.; Hoffmann F.. Dr. F. Hoffmann, Department of Ophthalmology, Univ. Hospital Benjamin Franklin, Free University of Berlin, Hindenburgdamm 30, 12203 Berlin, Germany. fhoffman@zedat.fu-berlin.de. Transplantation 76/10 (1511-1513) 27 Nov 2003.
Refs: 10.
ISSN: 0041-1337. CODEN: TRPLAU. Pub. Country: United States. Language: English. Summary Language: English.

AB Background. The novel immunomodulator, FTY720, mainly acts through sequestering of lymphocytes to secondary lymphatic tissue, thereby suppressing their infiltration into grafted organs. This study aimed to investigate its influence on corneal-**graft survival**.
Methods. Sixteen BALB/c mice (H-2d) received **corneal transplants** from C3H (H-2k) mice. Eight mice were treated with FTY720 (10 mg/kg per day) orally from day -1 to day 11, and all animals received 0.1% dexamethasone eye drops for the same time. In addition, eyes and regional lymph nodes from similarly treated animals were subjected to immunohistochemistry and proliferation assays. Results. FTY720 significantly prolonged **graft survival** from 28±8.1 to 36.5±7.1 days (P=0.021). In treated animals, corneal infiltration by CD4(+) and F4/ 80 (+) cells was reduced from 70.8±60.3 to 7.0±9.0 (P=0.004) and from 97.5±30.7 to 44.8±24.9 (P=0.01) cells, respectively, and allogeneic T-cell proliferation was decreased. Conclusions. FTY720 treatment substantially protects corneal allografts and may provide an immunomodulatory strategy in clinical corneal transplantation.

L6 ANSWER 3 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003173155 EMBASE An immunodominant minor histocompatibility alloantigen that initiates corneal allograft rejection. Haskova Z.; Sproule T.J.; Roopenian D.C.; Ksander B.R.. Dr. B.R. Ksander, Schepens Eye Research Institute, 20 Staniford Street, Boston, MA 02114, United States. ksander@vision.eri.harvard.edu. Transplantation 75/8 (1368-1374) 27 Apr 2003.
Refs: 23.
ISSN: 0041-1337. CODEN: TRPLAU. Pub. Country: United States. Language: English. Summary Language: English.

AB Background. Murine orthotopic corneal allografts experience immune privilege and have good survival as compared with skin allografts. However, privilege is not complete, and some grafts are still rejected. Unexpectedly, corneas expressing minor histocompatibility (H) alloantigens are rejected at a higher rate than major histocompatibility complex (MHC) disparate grafts. We hypothesize that certain immunodominant minor H alloantigens are extremely immunogenic when expressed in corneal tissue, terminate ocular immune privilege, and initiate corneal allograft rejection. Methods and Results. Corneal allograft survival and the role of

H3a+H3b were used for orthotopic corneas expressing either H3a or H3a+H3b experienced immune privilege and survived longer than skin allografts. By contrast, donor corneas expressing H3b (recognized by CD4+ T cells) experienced vigorous rejection and were eliminated faster than skin allografts. Conclusion. There are minor H alloantigens that terminate ocular immune privilege and initiate corneal allograft rejection. These minor H alloantigens are more immunogenic when expressed in corneal tissue than when they are expressed in skin allografts.

L6 ANSWER 4 OF 40 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:857158 The Genuine Article (R) Number: 727JF. Role of resident corneal leukocytes and draining cervical lymph nodes in corneal allograft rejection. Yamagami S (Reprint); Amano S. Univ Tokyo, Grad Sch Med, Dept Corneal Tissue Regenerat, Bunkyo Ku, 7-3-1 Hongo, Tokyo 1138655, Japan (Reprint); Univ Tokyo, Grad Sch Med, Dept Corneal Tissue Regenerat, Bunkyo Ku, Tokyo 1138655, Japan; Univ Tokyo, Grad Sch Med, Sect Corneal Transplantat, Bunkyo Ku, Tokyo 1138655, Japan. CORNEA (OCT 2003) Vol. 22, No. 7, Supp. [S], pp. S61-S65. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 0277-3740. Pub. country: Japan. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB We review recently published experimental evidence on **corneal transplant** immunology involving cornea and draining cervical lymph nodes (CLNs) in the mouse. In the cornea, major histocompatibility complex (MHC) class II- dendritic cells (DCs) are present in the corneal epithelium. These DCs can express MHC class II- antigen in vivo and in vitro. In the corneal stroma, there are many leukocytes of monocyte or macrophage lineage. Normal cornea has been reported to contain a significant number of bone marrow-derived resident cells, which may be able to act as antigen-presenting cells. Allograft rejection does not occur if draining CLNs are removed before corneal transplantation, indicative of an essential role of CLNs in promoting corneal allorejection. Moreover, donor cornea-derived DCs were detected in host draining CLNs in a mouse corneal transplantation **model**. These findings provide direct evidence that MHC class II- bone marrow-derived antigen-presenting leukocytes exist in the part of cornea used for transplantation and that direct allorecognition of antigen is, at least in part, relevant to the occurrence of corneal allograft rejection in which draining CLNs play a central role.

L6 ANSWER 5 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2002266142 EMBASE Effect of locally administered anti-CD154 (CD40 ligand) monoclonal antibody on survival of allogeneic **corneal transplants**. Qian Y.; Dana M.R.. Dr. M.R. Dana, Laboratory of Immunology, Schepens Eye Research Institute, Harvard Medical School, 20 Staniford Street, Boston, MA 02114, United States. dana@vision.eri.harvard.edu. Cornea 21/6 (592-597) 2002.
Refs: 30.
ISSN: 0277-3740. CODEN: CORNDB. Pub. Country: United States. Language: English. Summary Language: English.
AB Purpose. To determine the effect of ocular administration of anti-CD154 monoclonal antibody on the survival of orthotopic murine **corneal transplants**. Methods. BALB/c mice were used as recipients of multiple minor H- and MHC-mismatched orthotopic **corneal transplants**. Recipient beds were either avascular (normal-risk) or [illegible] Mice were randomized

in control mice to 90% in [illegible]
high-risk transplantation, the survival rate of anti-CD154-treated mice was enhanced to 55% compared with 0% in control mice at week 8 ($p = 0.0184$); however, tapering and termination of anti-CD154 led to some loss in **graft survival**, with a survival rate of 56% in normal-risk recipients, and 22% in high-risk recipients by week 20. Anti-CD40L treated animals displayed lower grades of post-operative corneal neovascularization ($p < 0.05$), in particular in normal-risk recipients. Conclusions. Local ocular administration of anti-CD154 is effective in the prevention of corneal allograft rejection in normal-risk recipients, and in delaying the incidence of rejection in high-risk recipients. Long-term **graft survival** may not be fully achieved following termination of the CD40-CD154 pathway blockade.

L6 ANSWER 6 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2002086044 EMBASE Intraocular dexamethasone delivery system for corneal transplantation in an animal **model**. Kagaya F.; Usui T.; Kamiya K.; Ishii Y.; Tanaka S.; Amano S.; Oshika T.. Dr. T. Oshika, Department of Ophthalmology, Univ. of Tokyo School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. oshika-tky@umin.ac.jp. Cornea 21/2 (200-202) 2002.
Refs: 14.
ISSN: 0277-3740. CODEN: CORNDB. Pub. Country: United States. Language: English. Summary Language: English.

AB Purpose. To assess the efficacy of a new intraocular biodegradable polymer dexamethasone drug delivery system (DEX DDS) in a high-risk corneal transplantation **model**. Methods. Lewis rats that received orthotopic **corneal transplants** (Balb/c mice donors) were divided into three groups (six rats in each); group 1 received no treatment and served as controls, group 2 was treated with 0.1% betamethasone eyedrops three times daily for 6 weeks, and group 3 received DEX DDS in the anterior chamber at the time of transplantation. Results. All grafts in the untreated control group were rejected within 8 days. In the betamethasone eyedrop group, five eyes (83%) were rejected during the 8-week study period. None of the grafts in the DEX DDS group was rejected. The administration of DEX DDS significantly prolonged the survival rate of the corneal grafts ($p < 0.001$, log-rank test). Conclusion. DEX DDS is effective in suppressing graft rejection in high-risk corneal transplantation.

L6 ANSWER 7 OF 40 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

2003:164950 Document No.: PREV200300164950. Survival of Second **Corneal Transplants**: An Experimental **Model**. Banerjee, S. [Reprint Author]; Nicholls, S. M.; Dick, A. D.. Ophthalmology, University of Bristol, Bristol, UK. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 2269. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: HLA typing is not routine in corneal transplantation. Therefore a precise correlation between accelerated rejection and antigens shared by first and subsequent donors bed has not been established. Moreover local factors such as properties of host bed affect the survival of corneal grafts. We performed a second corneal graft on either the ipsilateral or the contralateral eye to investigate the effect of sensitisation or local factors on **graft survival**. Methods: PVG(RT1c), [illegible] PVG strain rats

against allogeneic, syngeneic and third party after the second transplant. Results: There was no rejection of isografts. Accelerated rejection of LEW second grafts occurred in ipsilateral and contralateral eyes after both AO and LEW strains first grafts. Furthermore, survival of second grafts in the ipsilateral eye was reduced compared with the contralateral eye. Preliminary MLR results show secondary response to third party (AO strain) in animals previously exposed to LEW strain. Conclusion: 1. Accelerated rejection of second LEW allografts in the contralateral eye after an AO graft implies sensitisation to non MHC antigens shared by the first and second donor or shared or cross reactive MHC epitopes in AO and LEW strains. 2. The trend toward earlier ipsilateral second corneal allograft rejection compared to contralateral implies that local conditions, such as development of CALT and/or vascularisation are factors in accelerated rejection. Mismatching first and second donors may not prolong **graft survival**
.

L6 ANSWER 8 OF 40 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2003:143737 Document No.: PREV200300143737. Sentinel Detection Of Murine Aqueous And Subconjunctival Outflow By Colloidal Albumin. Hoffmann, F. [Reprint Author]; Franke, J.; Zhang, E. -P. [Reprint Author]. Ophthalmology, Free University of Berlin-UKBF, Berlin, Germany. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 2216. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: To explore and modulate the lymphatic drainage system and to determine its influence on corneal **graft survival** in mice. Methods: Two microliters of 99mTC colloidal albumin (Nanocoll(R)) were injected into the anterior chamber of the left eye of 6 BALB/c mice. Four groups of 6 mice received subconjunctival Nanocoll(R) injections. The submandibular lymph nodes were removed either on the left 7 or 21 days prior to Nanocoll(R) injection or bilaterally 7 days beforehand. Twenty-four hours later blood was obtained from each animal by heart puncture. The right and left eyes, the right and left submandibular lymph nodes and the spleen and liver were removed. The probes were weighed, and radioactivity was measured by a well-type NaI(TI) gamma scintillation detector (Baird Atomic). A standard probe was measured for each animal to calculate the radioactivity per mg of tissue or ml of blood corresponding to 106 counts per minute of the injected suspension. Four further groups of 6 BALB/c mice each received an orthotopic **corneal transplant** from C3H mice. Three of these groups underwent preoperative submandibular lymphadenectomy as in the above-mentioned tracer experiments. Results: Radioactivity was detected as follows: 90.7% in the liver, 7.5% in the spleen and 1.1% in the left lymph node after intracameral Nanocoll injection; 25.2% in the liver, 1.5% in the spleen and 71.6% in the regional lymph node after subconjunctival injection. The count rate/min/mg of tissue was about five times higher in the left than in the right submandibular lymph node after intracameral injection ($p<0.01$). However, subconjunctival injection increased this factor to 200. Removal of the left submandibular lymph node dramatically increased the count rate in the right submandibular lymph node ($p<0.01$). Bilateral lymphadenectomy increased the count rate in the blood ($p<0.01$) and spleen (p0.05). In three animals of group 4 the transplant was clear on day 35. Conclusion: Our data confirm functional lymphatic drainage via the uveoscleral pathway and conjunctiva in mice. The more intensive lymphoid

allograft rejection in mice. Hoffmann F.; [illegible]
F.; Foss H.-D.; Franke J.; Coupland S.E.. F. Hoffmann, Department of Ophthalmology, Univ. Hospital Benjamin Franklin, Free University Berlin, Hindenburgdamm 30, 12203 Berlin, Germany. fhoffman@zedat.fu-berlin.de. Graefe's Archive for Clinical and Experimental Ophthalmology 239/11 (850-858) 2001.
Refs: 24.
ISSN: 0721-832X. CODEN: GACODL. Pub. Country: Germany. Language: English. Summary Language: English.

AB Purpose: To modulate aqueous outflow via the uveoscleral pathway and to determine its influence on corneal **graft survival** in mice. Methods: BALB/c mice received **corneal transplants** from C3H mice and were placed randomly in three treatment groups: saline, pilocarpine or latanoprost. Three further groups received adjuvant systemic and topical corticosteroids. The kinetics of infiltrating lymphocytes, neutrophils and macrophages in the transplants was investigated in an additional 96 animals. Cytokine expression in the submandibular lymph nodes and spleen was investigated using in-situ hybridization and RNAse protection assay. Tracer experiments were conducted using (99m)TC colloidal albumin Nanocoll; count rates were determined in the submandibular lymph nodes, spleen and blood following both subconjunctival and intracameral injection. Results: Neither pilocarpine nor latanoprost had any influence on aqueous outflow or allograft survival in mice. Neutrophils and macrophages dominated the infiltrating cells 11 days postoperative in both treated and untreated grafts. On postoperative day 13, a greater increase in lymphocytes than in other cell groups was observed in allogeneic grafts. Following allogeneic transplantation, 1% of lymphocytes in ipsilateral submandibular lymph nodes were positive for IFN-γ. Tracer studies revealed a 16% aqueous outflow via the uveoscleral routes following intracameral injection of Nanocoll; this was increased by 97% with subconjunctival injection. Conclusion: Our data confirm the existence of functional lymphatic drainage via the uveoscleral pathway and conjunctiva in the mouse. Cells within the ipsilateral submandibular lymph node respond to stimuli upstream. This reaction could potentially be manipulated to improve **graft survival**.

L6 ANSWER 10 OF 40 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:278806 Document No.: PREV200100278806. Capacity to regulate early development of allo-response in **corneal transplant** by ACAID induction in long-term graft acceptors. Maruyama, K. [Reprint author]; Yamada, J. [Reprint author]; Sano, Y. [Reprint author]; Kinoshita, S. [Reprint author]. Ophthalmology, Kyoto Prefectural Univ. of Med, Kyoto, Japan. IOVS, (March 15, 2001) Vol. 42, No. 4, pp. S469. print.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. April 29-May 04, 2001.
Language: English.

L6 ANSWER 11 OF 40 MEDLINE on STN
2002128581. PubMed ID: 11864435. An experimental study on subconjunctival interleukin-1 receptor antagonist for promotion of **corneal transplant** survival. Zhai C; Zhang W; Zou L; Pan Z; Li N; Wu Y; Lu L; Zhang S; Ma D. (Beijing Institute of Ophthalmology, Beijing 100005, China.) [Zhonghua yan ke za zhi] Chinese journal of ophthalmology, (2001 Jul) 37 (4) 270-2. Journal code: 16210540R. ISSN: 0412-4081. Pub. country: China. Language: Chinese.

AB OBJECTIVE: To determine whether the subconjunctival application of

of 0.9% normal saline instead for consecutive [illegible] were evaluated for 4 weeks after surgery for signs of rejection. RESULTS: The mean survival time (MST) of the grafts of the experimental groups was increased significantly ($t = 0.00$, $P < 0.01$) in comparison with the control group. The MST of the IL-1ra 200 microg group was increased significantly than that of the IL-1ra 50 microg group ($t = 0.00$, $P < 0.01$). Furthermore, the IL-1ra-treated grafts had significantly less corneal inflammation, infiltration, lower levels of opacity, edema, neovascularization and rejection index compared with the control group. CONCLUSIONS: Subconjunctival treatment of IL-1ra has a significantly positive effect on promoting corneal allograft survival. And its effect is dosage-dependent.

L6 ANSWER 12 OF 40 MEDLINE on STN
2003509242. PubMed ID: 14585142. Molecular mechanisms of immunity in corneal allotransplantation and xenotransplantation. Qian Y; Dana M R. (Laboratory of Immunology, Schepens Eye Research Institute, Harvard Medical School, 20 Staniford Street, Boston, MA 02114, USA.. yqian@vision.eri.harvard.edu) . Expert reviews in molecular medicine [electronic resource], (2001 Jul 16) 2001 1-21. Journal code: 100939725. ISSN: 1462-3994. Pub. country: England: United Kingdom. Language: English.

AB Corneal allotransplantation is the most common and successful form of solid organ transplantation in humans. In uncomplicated cases, the two-year **graft survival** rate is over 90%. This extraordinary success can be attributed in part to various features of the normal cornea and anterior segment that together account for their 'immune-privileged' status. However, despite this success, a significant number of corneal grafts fail and immunological rejection remains by far the leading cause of graft failure. Studies on animal **models** of corneal transplantation have yielded a wealth of information on the molecular and cellular features of graft rejection, and have established that this process is mediated primarily by CD4+ T cells of the T helper 1 (Th1) phenotype. In addition, studies have elucidated that certain facets of allosensitisation differ between corneal and other solid organ transplants. On the basis of these findings, novel experimental strategies selectively targeting the afferent or efferent arms of corneal alloimmunity have provided promising results in preventing corneal allograft rejection in the laboratory. Finally, because of the global shortage of human donor corneas, there is currently renewed interest in the possibility of using corneas from other species for transplantation into human eyes (xenotransplantation). Preliminary studies on animal **models** of corneal xenotransplantation have documented both antibody-mediated and cell-mediated responses that might play important roles in the accelerated rejection observed in corneal xenotransplants. This review synthesises the principal concepts emerging from studies of the molecular mechanisms in **corneal transplant** immunology.

L6 ANSWER 13 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
2001:758173 Document No. 136:165572 Molecular mechanisms of immunity in corneal allotransplantation and xenotransplantation. Qian, Ying; Reza, Dana M. (Lab. Immunology, Schepens Eye Res. Inst., Harvard Medical School, Boston, MA, 01114, USA). Expert Reviews in Molecular Medicine [online computer file] No pp. given (English) 2001. CODEN: ERMMFS. ISSN: 1462-3994. URL: http://www-ermm.cbcu.cam.ac.uk/01003246a.pdf Publisher: Cambridge University Press.

AB A review. Corneal allotransplantation is the most common and successful

cause of graft failure. Studies on animal models transplantation have yielded a wealth of information on the mol. and cellular features of graft rejection, and have established that this process is mediated primarily by CD4+ T cells of the T helper 1 (Th1) phenotype. In addition, studies have elucidated that certain facets of allosensitization differ between corneal and other solid organ transplants. On the basis of these findings, novel exptl. strategies selectively targeting the afferent or efferent arms of corneal alloimmunity have provided promising results in preventing corneal allograft rejection in the laboratory Finally, because of the global shortage of human donor corneas, there is currently renewed interest in the possibility of using corneas from other species for transplantation into human eyes (xenotransplantation). Preliminary studies on animal **models** of corneal xenotransplantation have documented both antibody-mediated and cell-mediated responses that might play important roles in the accelerated rejection observed in corneal xenotransplants. This review synthesizes the principal concepts emerging from studies of the mol. mechanisms in **corneal transplant** immunol.

L6 ANSWER 14 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
2000:335262 Document No. 132:339388 Local use of soluble tumor necrosis receptor I (sTNFRI) for prophylaxis and treatment of **corneal transplant** rejection and other disorders of the eye. Dana, M. Reza (The Schepens Eye Research Institute, Inc., USA). PCT Int. Appl. WO 2000027421 A2 20000518, 36 pp. DESIGNATED STATES: W: AU, CA, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US26262 19991105. PRIORITY: US 1998-PV107351 19981106.

AB Topical application of sTNFRI antagonist promotes **corneal transplant** survival in a murine **model** of orthotopic allotransplantation, having a significant effect in prolonging **graft survival**. Furthermore, the promotion of **graft survival** is associated with a significant decrease in corneal inflammation. Therefore, sTNFRI and related antagonists to tumor necrosis factor-α activity can be used in a therapeutic composition for local prophylaxis and treatment of allograft rejection and a wide array of immunogenic inflammatory diseases of the eye. The composition comprises a therapeutically effective amount of a tumor necrosis factor-α antagonist in association with a pharmaceutically acceptable carrier vehicle for local application. The effect of topical soluble TNFR-I on the survival of minor H-disparate **corneal transplants** was investigated. Corneal grafts treated with sTNFR1 exhibited improved survival rates of 86.2 and 78.4% at week 4 and 8, resp. The enhancement in corneal allograft acceptance by topical sTNFR1 treatment is statistically significant.

L6 ANSWER 15 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 1
2000423543 EMBASE Interleukin-1 receptor antagonist therapy and induction of anterior chamber-associated immune deviation-type tolerance after corneal transplantation. Yamada J.; Zhu S.-N.; Streilein J.W.; Dana M.R.. M.R. Dana, Laboratory of Immunology, Schepens Eye Research Institute, 20 Staniford Street, Boston, MA 02114, United States. dana@vision.eri.harvard.edu. Investigative Ophthalmology and Visual Science 41/13 (4203-4208) 2000.
Refs: 14.
ISSN: 0146-0404. CODEN: IOVSDA. Pub. Country: United States. Language:

deviation (ACAID), which has been shown to [illegible]
survival of **corneal transplants**. METHODS. Corneal buttons from BALB/c (syngeneic) or C57BL/6 (fully mismatched allogeneic) mice were orthotopically grafted onto BALB/c recipients. Topical IL-1ra or vehicle alone was applied to grafts three times daily. Donor-specific ACAID was measured in allogeneic grafted mice at 4 and 8 weeks after transplantation by ear-challenging grafted hosts with donor-derived splenocytes 1 week after SC immunization. In separate experiments, grafted mice were treated for 4 weeks before injecting ovalbumin (OVA) into their anterior chambers to determine their capacity to induce antigen-specific ACAID. RESULTS. Treatment with IL-1ra did not promote, or inhibit, induction of donor-specific ACAID compared with vehicle-treated controls at either the early or late time points studied. However, IL-1ra treatment after transplantation led to significantly earlier restoration of the grafted eyes' capacity for inducing ACAID to soluble antigen (OVA). CONCLUSIONS. Promotion of OVA-specific ACAID by IL-1ra suggests that suppression of IL-1-mediated mechanisms contributes to recovery of the anterior segment's immunosuppressive microenvironment at least 1 month earlier than would otherwise be seen after corneal transplantation. However, IL-1ra treatment does not alter induction of donor-specific ACAID after transplantation, suggesting that its anti-inflammatory activities do not lead to an ACAID-inducing signal per se. This suggests that IL-1ra promotes **graft survival** almost exclusively by virtue of suppressing inflammation and not by directly promoting tolerance or antigen-specific regulatory pathways.

L6 ANSWER 16 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2000431917 EMBASE Topical soluble tumor necrosis factor receptor type I suppresses ocular chemokine gene expression and rejection of allogeneic **corneal transplants**. Qian Y.; Dekaris I.; Yamagami S.; Dana M.R.. Dr. M.R. Dana, Schepens Eye Research Institute, Harvard Medical School, 20 Staniford St, Boston, MA 02114, United States. dana@vision.eri.harvard.edu. Archives of Ophthalmology 118/12 (1666-1671) 2000.
Refs: 50.
ISSN: 0003-9950. CODEN: AROPAW. Pub. Country: United States. Language: English. Summary Language: English.

AB Objective: To determine the effect of topical soluble tumor necrosis factor receptor type I (sTNFR-I) on survival of murine orthotopic **corneal transplants** and on ocular chemokine gene expression after corneal transplantation. Methods: BALB/c mice (N=50) were used as recipients of multiple minor H-disparate **corneal transplants** from B10.D2 donors. After orthotopic corneal transplantation, mice were randomized in a masked fashion to receive either topical sTNFR-I or vehicle 3 times daily, and all grafts were evaluated for signs of rejection and neo-vascularization by slitlamp biomicroscopy for 8 weeks. Ocular chemokine gene expression in sTNFR-I-and vehicle only-treated groups was determined using a multiprobe ribonuclease protection assay. Results: Hosts treated with topical sTNFR-I experienced significantly enhanced corneal allograft survival compared with animals treated with vehicle alone (P = .01). Moreover, postoperative messenger RNA levels of RANTES and macrophage inflammatory protein-1β in sTNFR-I-treated eyes were substantially suppressed compared with vehicle-treated eyes. Vehicle-treated eyes bearing rejected allografts expressed higher levels of messenger RNA for both chemokines than control eyes bearing accepted allografts. Conclusions: Topical treatment with

immunosuppressive drugs.

L6 ANSWER 17 OF 40 MEDLINE on STN DUPLICATE 2
2000216345. PubMed ID: 10755569. ICAM-1 deficiency suppresses host allosensitization and rejection of MHC-disparate **corneal transplants**. Zhu S N; Yamada J; Streilein J W; Dana M R. (Laboratory of Immunology, Schepens Eye Research Institute, Harvard Medical School, Boston, Massachusetts, USA.) Transplantation, (2000 Mar 15) 69 (5) 1008-13. Journal code: 0132144. ISSN: 0041-1337. Pub. country: United States. Language: English.

AB BACKGROUND: We used a murine **model** of orthotopic corneal transplantation to determine whether host deficiency in ICAM-1 promotes survival of corneal grafts with different degrees of allodisparity. METHODS: ICAM-1-/- and wild-type C57BL/6 (ICAM-1+/+) received corneal grafts from the following strains of mice: BALB/c (fully mismatched), BALB.b (mismatched at multiple minor H only), or B10.D2 [including major histocompatibility complex (MHC) mismatch]. Graft rejection, induction of allospecific delayed-type hypersensitivity (DTH) responses, and leukocytic infiltration of grafts were measured. RESULTS: There were no differences in long-term survival of allografts that were either fully mismatched or had only minor H disparity in ICAM-1+/+ vs. ICAM-1-/-hosts. However, whereas B10.D2 grafts were accepted in only 58% of the ICAM-1+/+ hosts, **graft survival** in ICAM-1-/- recipients was 100% (P=0.006). Moreover, none of the ICAM-1-/- mice receiving B10.D2 grafts developed allospecific DTH. CONCLUSIONS: Prolonged survival seen in MHC-mismatched grafts in ICAM-1-/- mice, along with a suppressed DTH response to donor alloantigens after transplantation, suggest that ICAM-1 is associated with recipient sensitization to MHC alloantigens.

L6 ANSWER 18 OF 40 MEDLINE on STN DUPLICATE 3
2000440889. PubMed ID: 10972223. Beneficial effect of HLA-DR matching on the survival of corneal allografts. Volker-Dieben H J; Claas F H; Schreuder G M; Schipper R F; Pels E; Persijn G G; Smits J; D'Amaro J. (Department of Ophthalmology, Vrije Universiteit, Amsterdam, The Netherlands.) Transplantation, (2000 Aug 27) 70 (4) 640-8. Journal code: 0132144. ISSN: 0041-1337. Pub. country: United States. Language: English.

AB BACKGROUND: Although HLA typing and matching have been used for 3 decades, that practice has been poorly implemented in corneal transplantation, mainly because of inconclusive or contradictory analytical results. Consequently, we studied the immune response of **corneal transplant** recipients to HLA histoincompatibilities in a large homogeneous study. METHODS: All corneal transplantations performed by a single surgeon between 1976 and 1996 were studied. HLA-AB matching was used for recipient selection. All HLA typings were performed by a single experienced laboratory. Population genetic techniques were used to assess the validity of the HLA typings. Mono- and multivariate analyses were performed to identify the factors which significantly influence the survival of corneal allografts. Simulation studies were carried out to demonstrate the effects of mis-typed donor and recipient HLA-DR typings on analytical results. RESULTS: Retransplantation, degree of vascularization, HLA-AB and DR matching, endothelial cell count, graft size, recipient gender, and storage method were identified as significant factors by our monovariate analyses. A Cox proportional hazards survival analysis **model** identified degree of vascularization and HLA-AB and DR matching as significant prognostic factors when all immunological rejection episodes were used, P=0.000001. When only irreversible immunological rejection episodes were used, panel reactive antibodies,

L6 ANSWER 19 OF 40 MEDLINE on STN
2000019764. PubMed ID: 10551999. Beneficial effect of preoperative mycophenolate mofetil in murine corneal transplantation. Reis A; Spelsberg H; Reinhard T; Braunstein S; Godehardt E; Sundmacher R. (Eye Clinic, Heinrich-Heine University, Moorenstr. 5, D-40 225 Duesseldorf, Germany.. reis@uni-duesseldorf.de) . Transplant international : official journal of the European Society for Organ Transplantation, (1999) 12 (5) 341-5. Journal code: 8908516. ISSN: 0934-0874. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB To investigate the effect of preoperative mycophenolate mofetil (MMF) on allograft survival in a murine corneal transplantation **model**. Corneal grafting was performed from Brown Norway to Lewis rats. Groups were divided as follows: Rats that received syngeneic or allogeneic grafts without therapy served as controls. MMF treatment was either started 7 days prior to transplantation and continued for 14 postoperative days (POD) or started at the day of corneal grafting until POD 14. MMF (20 mg/kg) administered postoperatively had no significant beneficial effect on corneal **graft survival** when compared with controls. However, the group receiving 40 mg/kg MMF postoperatively showed a statistically significant prolonged **graft survival**. A 1-week preoperative administration of 20 mg/kg MMF allowed superior **graft survival**. Priming the immune system of **corneal transplant** recipients preoperatively with MMF proved to be a beneficial therapeutic regimen for prolonging corneal allograft survival in rats.

L6 ANSWER 20 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
1998:351781 Document No. 129:40160 Local use of IL-1ra in **corneal transplant** rejection or disorders of the eye. Dana, M. Reza (Schepens Eye Research Institute, Inc., USA; Dana, M. Reza). PCT Int. Appl. WO 9822130 A1 19980528, 43 pp. DESIGNATED STATES: W: AU, BR, CA, CN, CZ, IL, JP, KR, MX, NO, SG, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US21393 19971119. PRIORITY: US 1996-752075 19961119.

AB Topical application of interleukin-1 receptor antagonist (IL-1ra) is shown to promote **corneal transplant** survival in a murine **model** of orthotopic allotransplantation, having a significant effect in prolonging **graft survival** in both high-risk and normal (low-risk) stromal beds. Furthermore, the promotion of **graft survival** is associated with a significant decrease in corneal inflammation. Therefore, IL-1ra and related antagonists to interleukin-1 can be used in a therapeutic composition for topical prophylaxis and treatment of allograft rejection and for local treatment of a wide array of immunogenic inflammatory diseases of the eye. The composition comprises a therapeutically effective amount of IL-1ra in association with a pharmaceutically acceptable carrier vehicle for topical application.

L6 ANSWER 21 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
1999011021 EMBASE Effect of a topically applied neutralizing antibody against vascular endothelial growth factor on corneal allograft rejection of rat. Yatoh S.; Kawakami Y.; Imai M.; Kozawa T.; Segawa T.; Suzuki H.; Yamashita K.; Okuda Y.. Dr. Y. Okuda, Division of Endocrinology/Metabolism, Institute of Internal Medicine, University of Tsukuba, 1-1-1 Tennodai Tsukuba, Ibaraki 305, Japan. Transplantation 66/11 (1519-1524) 15 Dec 1998.
Refs: 18.

infiltration into the graft, we considered the p... endothelial growth factor (VEGF), a potent permeability-increasing factor and angiogenesis-mediating factor, could participate in the immune response. Methods. As the established **corneal transplant model** for rejection, the **corneal transplant** between Lewis and Fisher rats has been reported. First, we evaluated VEGF production in the graft by immunohistochemical method in the animal **model**. Next, we tried to neutralize the effect of VEGF by topical administration of anti-VEGF antibody. We administered anti-VEGF antibody as eye drops for 10 days just after the transplantation of the established animal **corneal transplant model**. Results. VEGF was strongly produced from the infiltrative cells into the graft. Anti-VEGF antibody significantly suppressed the acute rejection compared with saline or rabbit IgG. Conclusions. The inhibition of VEGF by topically applied neutralizing antibody is a new potential therapeutic strategy for the treatment of corneal transplantation.

L6 ANSWER 22 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

1998349203 EMBASE Interleukin 1 receptor antagonist suppresses allosensitization in corneal transplantation. Yamada J.; Dana M.R.; Zhu S.-N.; Alard P.; Streilein J.W.. Dr. M.R. Dana, Schepens Eye Research Institute, 20 Staniford St, Boston, MA 02114, United States. Archives of Ophthalmology 116/10 (1351-1357) 1998.
Refs: 38.
ISSN: 0003-9950. CODEN: AROPAW. Pub. Country: United States. Language: English. Summary Language: English.

AB Objective: To delineate the mechanisms by which topical interleukin I receptor antagonist (IL-1RA) treatment promotes orthotopic corneal allograft survival. Methods: Corneal buttons were prepared from eyes of C57BL/6 mice and placed orthotopically in normal or neovascularized (high-risk) eyes of BALB/c mouse recipients. Topical IL-1RA (or vehicle alone) was applied to grafts 3 times daily until the grafted eyes were enucleated. Corneal specimens were evaluated for content of Langerhans cells. A week after enucleation, I group of recipients was tested for allospecific delayed-type hypersensitivity elicited by intrapinnae injections of donor splenocytes. In companion experiments, a second group of mice that underwent transplantation, IL-1RA treatment, and enucleation was challenged with orthotopic skin grafts from B10.D2 donor mice (sharing minor H antigens with C57BL/6 mice) to determine whether the second group of mice could reject grafts bearing corneal donor minor H alloantigens in an accelerated fashion. Results: Mice whose orthotopic corneal allografts were treated topically with IL-1RA acquired neither donor-specific delayed-type hypersensitivity ($P<.001$) nor the capacity to reject orthotopic donor-type skin allografts in an accelerated manner ($P<.05$), whereas controls treated with vehicle alone developed delayed-type hypersensitivity and rejected B10.D2 grafts in an accelerated manner. Moreover, IL-1RA-treated grafts placed in both high-risk ($P = .01$) and normal-risk ($P = .004$) eyes displayed significantly reduced levels of infiltrating Langerhans cells compared with vehicle-treated controls. Conclusions: Topical IL-1RA promotes corneal allograft survival in large part by preventing activity of recipient Langerhans cells, and thereby preventing these cells from inducing systemic allosensitization. These data suggest that IL-1 plays a key role in promoting allosensitization when corneal allografts are placed orthotopically. Clinical Relevance: Suppression of allosensitization by topical IL-1RA may prove a clinically useful method for enhancing **corneal transplant**

Boston, Massachusetts 02114, USA.) Transplantation, [illegible]
1501-7. Journal code: 0132144. ISSN: 0041-1337. Pub. country: United States. Language: English.

AB BACKGROUND: Interleukin (IL)-1 is a potent proinflammatory cytokine that plays a critical role in initiating and maintaining immunogenic inflammation. We performed a series of experiments to determine whether the topical application of IL-1 receptor antagonist (IL-1ra) can prolong **corneal transplant** survival in the murine **model** of orthotopic allotransplantation. METHODS: For all experiments, C57BL/6 corneas were transplanted into BALB/c (major histocompatibility and minor histocompatibility-disparate) eyes. "High-risk" transplants were transplants that had been sutured into BALB/c recipient beds with corneal neovascularization induced by placement of three interrupted sutures in the host cornea 2 weeks earlier. Both risk groups were divided in a masked fashion into treatment subgroups that received either 20 mg/ml of IL-1ra mixed in 0.2% sodium hyaluronate vehicle (n=28) or placebo alone (n=25). All transplants were evaluated for 8 weeks after surgery for signs of rejection. At the end of follow-up, corneal specimens were processed for enumeration of Langerhans cells and histopathological evaluation. RESULTS: Survival rates of both normal-risk and high-risk transplants increased significantly among the IL-1ra-treated animals compared with untreated controls by both stratified Mantel-Haenszel (P=0.02) and Kaplan-Meier survival (P=0.03) analyses. Furthermore, both normal- and high-risk IL-1ra-treated grafts had significantly less inflammation and Langerhans cells infiltration compared with untreated controls. CONCLUSIONS: Topical treatment with IL-1ra has a significantly positive effect in promoting corneal allograft survival.

L6 ANSWER 24 OF 40 MEDLINE on STN DUPLICATE 5

1998084912. PubMed ID: 9422933. Oral immunisation as a strategy for enhancing corneal allograft survival. Ma D; Mellon J; Niederkorn J Y. (Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas 75235-9057, USA.) British journal of ophthalmology, (1997 Sep) 81 (9) 778-84. Journal code: 0421041. ISSN: 0007-1161. Pub. country: ENGLAND: United Kingdom. Language: English.

AB AIMS: To determine optimal conditions for enhancing corneal allograft survival through oral administration of donor specific corneal cells. METHODS: A mouse **model** of penetrating keratoplasty was used to evaluate the efficacy and optimal conditions for preventing immunological rejection of corneal allografts. C3H corneal grafts were transplanted orthotopically to CB6F1 recipients and represented mismatches at the entire major histocompatibility complex (MHC) and multiple minor histocompatibility loci. Tissue cultured C3H corneal epithelial and endothelial cells were administered orally to CB6F1 mice before or shortly after the application of orthotopic C3H corneal allografts. Cultured C3H corneal cells were conjugated with the non-toxic B subunit of cholera toxin as a means of preferentially inducing oral tolerance. RESULTS: Ten oral doses of donor cells administered before keratoplasty reduced the incidence of corneal graft rejection from 100% in untreated hosts to 54% in orally tolerised mice. Conjugation of cholera toxin to corneal cells significantly enhanced the efficacy of oral tolerance such that only 9% of the mice fed 10 doses of cholera toxin conjugated cells rejected their corneal grafts. Even a single oral inoculation of corneal cells conjugated to cholera toxin was able to reduce corneal graft rejection by 36%. CONCLUSIONS: Oral administration of donor specific cells greatly enhances corneal **graft survival**. Use of cholera toxin adjuvant markedly enhances the efficacy of oral tolerance such that even a

1998084901. PubMed ID: 9422922. [illegible]
large series of **corneal transplants** in India. Dandona L; Naduvilath T J; Janarthanan M; Ragu K; Rao G N. (Public Health Ophthalmology Service, L V Prasad Eye Institute, Hyderabad, India.) British journal of ophthalmology, (1997 Sep) 81 (9) 726-31. Journal code: 0421041. ISSN: 0007-1161. Pub. country: ENGLAND: United Kingdom. Language: English.

AB AIM/BACKGROUND: The public health significance of corneal transplantation in dealing with corneal blindness in the developing world would depend upon the survival rate of transplants. This study was done to analyse the survival rate of **corneal transplants** in a large series in India, and to evaluate the influence of various risk factors on transplant survival. METHODS: The records of a series of 1725 cases of **corneal transplants** carried out during 1987-95 at a tertiary eye care institution in India were reviewed. The Kaplan-Meier method was used to determine 5 year survival rates of **corneal transplants** performed for the various categories of preoperative diagnosis. Multivariate Cox proportional hazards regression was used to assess how preoperative diagnosis, socioeconomic status, age, sex, vascularisation of host cornea, quality of donor cornea, and training status of surgeon influenced transplant survival. The effect of these variables on visual outcome was assessed using multiple logistic regression. RESULTS: The survival rates at 1, 2, and 5 years for all **corneal transplants** performed for the first time in 1389 cases were 79.6% (95% confidence interval = 77.3-81.9%), 68.7% (65.7-71.7%) and 46.5% (41.7-51.3%). The 5 year survival rate was highest if the **corneal transplant** was done for keratoconus (95.1% (84.8-100%)) and lowest if carried out for previous transplant failure (21.2% (13.8-28.6%)). The relative risk of transplant failure was higher if the preoperative diagnosis was previous transplant failure (2.04 (1.62-2.55)), aphakic bullous keratopathy (1.78 (1.38-2.28)), corneal clouding due to miscellaneous causes including congenital conditions and glaucoma (1.63 (1.21-2.19)), or adherent leucoma (1.11 (0.81-1.51)) than for the other preoperative diagnoses. Patients with lower socioeconomic status had higher relative risk of transplant failure (1.28 (1.16-1.42)), as did patients < 10 years of age (1.42 (1.23-1.64)). Higher relative risk of transplant failure was associated with vascularisation of the host cornea before transplantation (1.15 (1.04-1.27)), and with the use of fair quality donor cornea for transplantation compared with excellent, very good, or good quality donor cornea (1.26 (1.06-1.52)). Before **corneal transplant** 80.2% of the eyes were blind (visual acuity < 3/60), whereas at last follow up 41.8% eyes were blind. The odds of having visual acuity > 6/18 were higher if the transplant was done for keratoconus (9.99 (6.10-16.36)) or corneal dystrophies (1.77 (1.21-2.58)) than for the other preoperative diagnoses. CONCLUSION: Reasonable success with corneal transplantation is possible in the developing world if data from this part of the world regarding the different survival rates for the various preoperative diagnoses and the influence of risk factors on transplant survival and visual outcome are taken into account while determining priority for transplant cases in the present situation of limited availability of donor corneas.

L6 ANSWER 26 OF 40 MEDLINE on STN

1998009860. PubMed ID: 9349147. Conclusions of the **corneal transplant** follow up study. Collaborating Surgeons. Vail A; Gore S M; Bradley B A; Easty D L; Rogers C A; Armitage W J. (University of Leeds, Institute of Epidemiology and Health Services Research.) British journal

Multifactorial analysis of [illegible] Support Service from July 1987 to June 1991. RESULTS: Several recipient factors influencing **graft survival**, rejection, and visual acuity were identified, but no donor factors. Of the operative factors amenable to change, mixed suturing was associated with reduced **graft survival**, and larger grafts with increased risk of rejection but better visual acuity when surviving. There was increased risk of rejection with poor matching at HLA class I antigens, but mismatched HLA-DR grafts suffered less rejection than those with zero HLA-DR mismatches. Recipient age below 10 years was associated with increased risk of both rejection and graft failure. However, whereas increasing age above 10 years was not associated with differential **graft survival**, it was significantly associated with decreasing risk of rejection. CONCLUSIONS: While confirming possible benefits of HLA-A and B matching, the expense and delay involved in awaiting matched HLA-DR tissue is unlikely to be justified. Other donor factors are unrelated to graft outcome following screening of tissue by eye banks. The highest rates of graft failure and rejection happen in the early postoperative period, and factors influencing visual outcome are also apparent at this stage.

L6 ANSWER 27 OF 40 MEDLINE on STN DUPLICATE 6

97431126. PubMed ID: 9285225. Inhibition of corneal allograft reaction by CTLA4-Ig. Hoffmann F; Zhang E P; Pohl T; Kunzendorf U; Wachtlin J; Bulfone-Paus S. (Department of Ophthalmology, Benjamin Franklin Medical Center, Free University of Berlin, Germany.) Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie, (1997 Aug) 235 (8) 535-40. Journal code: 8205248. ISSN: 0721-832X. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB BACKGROUND: Activation of T cells requires both the interaction of T-cell receptor with major histocompatibility complex on the antigen-presenting cell and costimulatory signals, for instance the B7 antigens expressed on antigen-presenting cells and the CD28 molecule expressed on T cells. A recombinant fusion protein, CTLA4-Ig, has been produced that contains the extracellular domain of human CTLA4 fused to IgG1 constant region and that binds the B7 molecule with high affinity. Blocking the CD28/B7 interaction with CTLA4-Ig inhibits T cell activation in vitro and in vivo. METHODS: We used CTLA4-Ig in a fully MHC-mismatched mouse keratoplasty **model**. The animals were divided into four groups: (1) no treatment, (2) intraperitoneal treatment with 130 micrograms CTLA4-Ig, (3) intraperitoneal treatment with 300 micrograms CTLA4-Ig, (4) subconjunctival treatment with 290 micrograms CTLA4-Ig. RESULTS: The allograft reaction occurred in untreated animals between days 12 and 16 (mean 13.5). While topical application of CTLA4-Ig seemed to shorten the **graft survival** (mean 11.6 days) and systemic application of 130 micrograms had no influence (mean 14.0), only intraperitoneal injection of 300 micrograms of CTLA4-Ig prolonged the survival of allografts (mean > 20 days) ($P < 0.01$). CONCLUSION: CTLA4-Ig prolonged significantly the survival of corneal allografts in a fully MHC-mismatched mouse keratoplasty **model**, but the small antigen load of the **corneal transplant** and the anterior chamber-associated immune deviation (ACAID) may have a disadvantage to induce tolerance in this **model** of CTLA4-Ig therapy.

L6 ANSWER 28 OF 40 MEDLINE on STN DUPLICATE 7

97174338. PubMed ID: 9022072. CD95 ligand (FasL)-induced apoptosis is [illegible]

AB Although anatomical barriers and soluble mediators [illegible] immune privilege, it appears that the apoptotic cell death of Fas+ cells by tissue-associated CD95 ligand (Fas ligand, FasL) is an important component. One clinical example of the function of an immune privileged site is the success of human **corneal transplants**, where a very high percentage of transplants accept without tissue matching or immunosuppressive therapy. Since the mouse cornea expresses abundant Fas ligand and immune privilege has been implicated in the success of these transplants, we examined the role of FasL in corneal transplantation. Our results show that human corneas express functional FasL capable of killing Fas+ lymphoid cells in an in vitro culture system. Using a mouse **model** for corneal allograft transplantation, FasL+ orthografts were accepted at a rate of 45%, whereas FasL- grafts, or normal grafts transplanted to Fas- mice, were rejected 100% of the time. Histological analysis found that FasL+ grafts contained apoptotic mononuclear cells indicating the induction of apoptosis by the graft, while rejecting FasL- corneas contained numerous inflammatory cells without associated apoptosis. Taken together our results demonstrate that FasL expression on the cornea is a major factor in corneal allograft survival and, thus, we provide an explanation for one of the most successful tissue transplants performed in humans.

L6 ANSWER 29 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 8

97233731 EMBASE Document No.: 1997233731. Mechanism of concordant corneal xenograft rejection in mice: Synergistic effects of anti-leukocyte function-associated antigen-1 monoclonal antibody and FK506. Yamagami S.; Isobe M.; Yamagami H.; Hori J.; Tsuru T.. Dr. S. Yamagami, Department of Ophthalmology, Jichi Medical School, 3311-1 Yakushiji, Minami-kawachi, Kawachi-gun, Tochigi 329-04, Japan. Transplantation 64/1 (42-48) 1997. Refs: 35.
ISSN: 0041-1337. CODEN: TRPLAU. Pub. Country: United States. Language: English. Summary Language: English.

AB Background. The mechanisms of corneal xenogeneic immunoreaction, as well as the potential role of immunosuppressive therapy in the suppression of corneal xenograft rejection, have not been thoroughly explored. Methods. BALB/c mice who received orthotopic **corneal transplants** (Lewis rats donors) were administered intraperitoneally anti-leukocyte function associated antigen-1 (LFA-1) monoclonal antibody (mAb) or FK506 (3 mg/kg/day) or both of these immunosuppressants during a 12-day postoperative period. Histological (hematoxylin-eosin stain) and immunohistochemical evaluations of enucleated eyes were performed. Humoral immune response and delayed-type hypersensitivity (ear-swelling assay) were evaluated. Results. The mean (±SD) **graft survival** time in the untreated control, FK506-treated, anti- LFA-1 mAb-treated, and combined-treatment groups was 5.8±0.8, 9.4±4.0, 8.7±5.0, and 67.7±16.4 days, respectively. In the untreated control group, mouse IgG, IgM, and C3 were expressed on the rat corneal grafts during the early postoperative phase. Flow cytometry studies revealed high titers of xenoreactive IgG and IgM antibodies. T helper 1 cytokines were expressed on xenografted corneal beds, and delayed-type hypersensitivity was induced. However, local expression of IgM, C3 and T helper 1 cytokines, serum antibodies of IgG and IgM, and delayed-type hypersensitivity were suppressed in the anti-LFA-1 mAb- plus FK506-treated group. Conclusions. Both humoral and cell-mediated immune reaction play an important role in the initial rejection in rat-to-mouse corneal xenotransplantation. The treatment with anti-LFA-1 mAb in combination with

J.Y. Niederkorn, Department of Ophthalmology, [illegible]
University of Texas, 5323 Harry Hines Boulevard, Dallas, TX 75235-9057, United States. Investigative Ophthalmology and Visual Science 37/13 (2700-2707) 1996.
Refs: 41.
ISSN: 0146-0404. CODEN: IOVSDA. Pub. Country: United States. Language: English. Summary Language: English.

AB Purpose. To determine whether anterior chamber-associated immune deviation (ACAID) promotes corneal allograft survival. Methods. CB6F1 mice were grafted with orthotopic **corneal transplants** from C3H donors (mismatch at the entire major histocompatibility complex plus multiple major histocompatibility loci) and from NZB donors (mismatch only at multiple minor histocompatibility loci). ACAID was induced by priming in the anterior chamber (AC) with either Ia+ spleen cells, Ia+ spleen cells, corneal endothelial cells, or corneal epithelial cells from corneal allograft donors before orthotopic transplantation. The role of ACAID in promoting corneal allograft survival was examined by determining the fate of corneal allografts in splenectomized and eusplenic mice. Results. Anterior chamber priming produced a modest enhancement of the survival of fully allogeneic C3H corneal allografts. By contrast, AC priming with Ia- NZB spleen cells or NZB corneal endothelial cells results in the permanent acceptance of NZB corneal grafts in 60% and 90% of the CB6F1 hosts, respectively. Abolition of ACAID by splenectomy resulted in a sharp increase in the incidence of graft rejection in donor-host combinations involving multiple minor histocompatibility disparity. Conclusions. Anterior chamber priming with alloantigens promotes corneal allografts survival in nonimmune and preimmune hosts. Disruption of the camero-splenic axis prevents the induction of ACAID and greatly increases the risk for corneal allograft rejection.

L6 ANSWER 31 OF 40 MEDLINE on STN DUPLICATE 9
95184532. PubMed ID: 7878924. Negative effect of HLA-DR matching on **corneal transplant** rejection. Bradley B A; Vail A; Gore S M; Rogers C A; Armitage W J; Nicholls S; Easty D L. (University of Bristol Department of Transplantation Sciences, UK.) Transplantation proceedings, (1995 Feb) 27 (1) 1392-4. Journal code: 0243532. ISSN: 0041-1345. Pub. country: United States. Language: English.

L6 ANSWER 32 OF 40 MEDLINE on STN DUPLICATE 10
96002863. PubMed ID: 8529401. A subconjunctival degradable implant for cyclosporine delivery in **corneal transplant** therapy. Apel A; Oh C; Chiu R; Saville B; Cheng Y L; Rootman D. (Department of Ophthalmology, University of Toronto, Ontario, Canada.) Current eye research, (1995 Aug) 14 (8) 659-67. Journal code: 8104312. ISSN: 0271-3683. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The effect of local cyclosporine therapy upon **corneal transplant** survival was investigated. A high risk rabbit **model** with vascularized corneas was used to assess the efficacy of subconjunctivally implanted degradable devices for cyclosporine therapy. Animals were divided into four groups, receiving either no therapy, a placebo PLGA device, or drug containing devices implanted either at the time of transplantation or two weeks previous. The mean survival times of animals in the control and placebo groups were statistically equivalent (21 +/- 4 days vs 18 +/- 4 days). Devices containing CsA improved the survival time of grafts. Predosing the animals with CsA improved the survival time to 28 +/- 7 days, and CsA devices implanted at the time of transplantation increased the survival time to 35 +/- 7 days. The

on STN
95196295 EMBASE Document No.: 1995196295. Corneal neovascularization in rats as a **model** for photothrombotic therapy using bacteriochlorin a and an argon laser. Van Gool C.A.M.; Schuitmaker H.J.; Jager M.J.. Department of Ophthalmology, Academic Hospital Leiden, PO Box 9600,2300 RC Leiden, Netherlands. Graefe's Archive for Clinical and Experimental Ophthalmology 233/7 (435-440) 1995.
ISSN: 0721-832X. CODEN: GACODL. Pub. Country: Germany. Language: English. Summary Language: English.

AB Background: The presence of vessels has a negative influence on **corneal transplant** survival. Closure of such vessels prior to transplantation may improve the transplant results, and this might be achieved by irradiating the vessels with argon laser light after intravenous administration of a photo sensitizer, e.g. bacteriochlorin a (BCA). A suture-induced corneal neovascularization **model** in rats was set up to test this hypothesis. Methods: Suture-induced vessels in the cornea of male Wistar rats were irradiated with argon laser light after intravenous administration of BCA. We applied irradiation of varying energy levels and duration and assessed the changes in the vessels by slit-lamp examination, fluorescein angiography and histology. Results: Suture-induced corneal vessels in the rat could be used effectively to study photothrombosis therapy. Intravenous administration of BCA prior to irradiation (λ = 514.5 nm) of the corneal vessels led to vessel closure at lower energy levels and of longer duration than occurred with laser treatment alone. Conclusion: Suture-induced corneal neovascularization in the rat can be used as a **model** to study the efficacy of photothrombosis therapy. BCA can be used to enhance the rate and duration of vessel closure.

L6 ANSWER 34 OF 40 EMBASE
on STN
95068754 EMBASE Document No.: 1995068754. Apparent resistance to immunosuppression of MHC-matched **corneal transplants.** Nicholls S.M.; Bradley B.A.; Easty D.L.. Department of Ophthalmology, School of Medical Sciences, University Walk,Bristol BS8 1TD, United Kingdom. Transplantation 59/3 (325-328) 1995.
ISSN: 0041-1337. CODEN: TRPLAU. Pub. Country: United States. Language: English.

L6 ANSWER 35 OF 40 MEDLINE on STN DUPLICATE 11
94375224. PubMed ID: 8088966. Promotion of corneal allograft survival with leflunomide. Niederkorn J Y; Lang L S; Ross J; Mellon J; Robertson S M. (Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas 75235.) Investigative ophthalmology & visual science, (1994 Sep) 35 (10) 3783-5. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE. The efficacy of the antirejection drug leflunomide was evaluated in a rat **model** of penetrating keratoplasty. METHODS. Corneal grafts from inbred Lewis rats were transplanted orthotopically to inbred Wistar-Furth (WF) recipients. WF rats received either Leflunomide (HWA 486), the active metabolite of leflunomide (A77-1726A), or cyclosporin A, administered orally beginning 2 days before transplantation and continuing for 30 days thereafter. **Graft survival** was assessed clinically three times per week, and mean survival times were determined. RESULTS. Oral administration of either leflunomide or the salt of its active metabolite resulted in a significant prolongation of **graft survival** time. Moreover, almost one third of the grafts survived

L6 ANSWER 36 OF 40 EMBASE COPYRIGHT 2001 [illegible]
on STN
94268137 EMBASE Document No.: 1994268137. Suppression of corneal allograft rejection by systemic cyclosporine-A in heavily vascularized rabbit corneas following alkali burns. Rehany U.; Waisman M.. Department of Ophthalmology, Western Galilee Medical Center, P.O.B. 21,Nahariya 22100, Israel. Cornea 13/5 (447-453) 1994.
ISSN: 0277-3740. CODEN: CORNDB. Pub. Country: United States. Language: English. Summary Language: English.

AB Immunologic rejection is the main cause of corneal graft failure, especially in vascularized corneal beds. The purpose of this study was to investigate the effect of systemic Cyclosporine-A (CsA) on the survival of corneal allografts in heavily vascularized rabbit corneal beds, following alkali burn. Heavy corneal vascularization was induced in one eye of 20 rabbits by alkali burn. Forty-five days later, penetrating keratoplasty was performed in all the heavily vascularized corneas. Twenty-five mg/kg/day of CsA was intramuscularly administered to 10 rabbits for 30 days. The other 10 rabbits were treated with the solvent without CsA and were used as a matched control group. The results show a significant difference in corneal allograft survival between the two groups. All corneal grafts in the untreated group were intensely rejected and vascularized within 3 weeks. Nine of the 10 **corneal transplants**, in the CsA-treated group, remained transparent without signs of immunologic rejection for >180 days. In one **corneal transplant**, minor signs of rejection occurred. We suggest that CsA, when given systemically, is a potent drug in the prevention of immunologic rejection in high-risk corneal transplantations, such as allografts, in heavily vascularized corneas following alkali burn.

L6 ANSWER 37 OF 40 MEDLINE on STN
95001625. PubMed ID: 7918163. Penetrating keratoplasty in the United Kingdom: an interim analysis of the **corneal transplant** follow-up study. Bradley B A; Vail A; Gore S M; Rogers C A; Armitage W J; Nicholls S M; Easty D L. (University of Bristol, Department of Transplantation Sciences, United Kingdom.) Clinical transplants, (1993) 293-315. Journal code: 8812419. ISSN: 0890-9016. Pub. country: United States. Language: English.

AB 1. Clinical corneal transplantation has been performed for over a century, but many elements leading to a successful outcome have yet to be identified. 2. Because there are limitless supplies of tissue, the supply of corneas need never fall short of demand. Nevertheless, retrieval rates vary widely among regions in the UK due to uneven organization of services. 3. Organ culture of corneas improves the quality of transplanted tissues because it allows time for substandard material to be discarded. The outcome appears to equal other storage methods. 4. Between 1987 and 1991, 4,560 **corneal transplants** were performed by 428 surgeons at 216 centers in the UK and were registered with CTFS. Of these, 3,213 were evaluable for **graft survival**, rejection, and other measures of visual outcome. 5. Unifactorial analysis revealed that the percentage of **graft survival** at one year was 89% and rejection-free survival was 87%. However, the hazard of rejection appeared to increase at or after the time of suture removal. 6. The percentage of recipients in whom CVA was 6/24 or better (able to read normal text with correction) improved from 16% preoperatively to 59% at 3 and 70% at 12 months postoperatively overall. In patients transplanted purely for visual reasons, improvement was 78% and 83% at 3 and 12 months, respectively. 7. Interim results of

Astigmatism was investigated in 600 cases at 3 months postoperatively. Preliminary analysis indicated that the risk of severe astigmatism was influenced by suturing technique and large differences between (> 0.25 mm) donor and recipient trephine size. 9. The effects of HLA matching were evaluated in 542 transplants. HLA-A and B matching reduced the risk of rejection during the first 450 days posttransplant, but HLA-DR matching appeared to increase the risk of rejection. 10. A rat **model** designed to simulate clinical corneal grafting was used to investigate the interaction between immunosuppression and matching. Whereas MHC mismatching could be overcome with topical dexamethasone, non-MHC mismatching appeared resistant.(ABSTRACT TRUNCATED AT 400 WORDS)

L6 ANSWER 38 OF 40 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
93:713630 The Genuine Article (R) Number: MH917. CHANGING RISK FOR EARLY TRANSPLANT FAILURE - DATA FROM THE ONTARIO-CORNEAL-RECIPIENT-REGISTRY. CHIPMAN M L (Reprint); SLOMOVIC A S; ROOTMAN D; DIXON W S. UNIV TORONTO, DEPT PREVENT MED & BIOSTAT, TORONTO M5S 1A1, ONTARIO, CANADA; UNIV TORONTO, DEPT OPHTHALMOL, TORONTO M5S 1A1, ONTARIO, CANADA; CORNEAL RECIPIENT REGISTRY, TORONTO, ON, CANADA. CANADIAN JOURNAL OF OPHTHALMOLOGY-JOURNAL CANADIEN D OPHTALMOLOGIE (OCT 1993) Vol. 28, No. 6, pp. 254-258. ISSN: 0008-4182. Pub. country: CANADA. Language: ENGLISH. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB To examine the joint effects of donor, recipient and surgical characteristics on the risk of early **corneal transplant** failure, 73 cases of early failure (no period of clarity or clarity lasting no more than 28 days) reported to the Ontario Corneal Recipient Registry were compared with 1591 control transplants remaining clear for 6 months or more. In logistic regression **models** donor age was significantly associated with graft failure, with the odds of failure increasing by 24% per decade. In recipients with a history of cataract or glaucoma or with an intraocular lens in place the relative odds of failure ranged from 2.16 to 3.08. Among surgical factors, larger grafts increased risk by 45% per 0.25 mm. Grafts received before 1987 had a consistently higher risk of early failure than those received in 1987 or later. Concurrent changes in storage media, handling of donor tissue and management of recipients may have been responsible. We conclude that donor, recipient and surgical factors all contribute to the risk of early transplant failure.

L6 ANSWER 39 OF 40 MEDLINE on STN DUPLICATE 12
89289098. PubMed ID: 2661153. Effects of blood transfusion and cyclosporin on rabbit corneal **graft survival**. Liu E Y; Raizman M B; Rosner B; Ihley T M; Foster C S. (Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston.) Current eye research, (1989 May) 8 (5) 523-31. Journal code: 8104312. ISSN: 0271-3683. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Blood transfusion prolongs renal, cardiac, and skin allograft survival, but promotes rejection of bone marrow allografts. At present, it is unclear whether transfusion induces allograft tolerance or sensitization in **corneal transplants**. We performed eccentric penetrating keratoplasty on New Zealand albino rabbits, using Dutch rabbits as donors. Twenty-four recipient rabbits were randomly allocated into four groups. The control group received no pretreatment. The other three groups received a donor-specific whole-blood transfusion and/or cyclosporin seven days before the **corneal transplants**. A single blood transfusion accelerated allograft rejection by an average of 8.8 days ($p = 0.0005$). In contrast, a single cyclosporin pretreatment

transplants, our results raise the question whether blood transfusion can sensitize humans to corneal allografts.

L6 ANSWER 40 OF 40 MEDLINE on STN DUPLICATE 13
82055530. PubMed ID: 7028988. Potential role of cyclosporin A in corneal grafting. Hunter P A. Journal of the Royal Society of Medicine, (1981 Nov) 74 (11) 810-3. Journal code: 7802879. ISSN: 0141-0768. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The immunosuppressive drug cyclosporin A has been shown to be effective in preventing corneal allograft reactions in rabbits when administered by intramuscular injection. However, when used systemically in man, the drug may have potentially serious side effects and a series of experiments has therefore been performed in order to investigate the use of topically applied cyclosporin A in rabbit **corneal transplants**. Using a single set **model** of the corneal allograft reaction, two groups of rabbits treated with topically applied cyclosporin A for periods of four and thirteen weeks respectively showed significantly increased **graft survival** compared with untreated controls (P less than 0.001).

=> s VEGFR-3 inhibitor
L9 12 VEGFR-3 INHIBITOR

=> dup remove l9
PROCESSING COMPLETED FOR L9
L10 11 DUP REMOVE L9 (1 DUPLICATE REMOVED)

=> d l10 1-11 cbib abs

L10 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2004:36626 Document No. 140:93929 Preparation of N-(pyridinylmethyl)anthranilamides as VEGFR-2 and **VEGFR-3 inhibitors** for treating diseases caused by persistent angiogenesis. Huth, Andreas; Krueger, Martin; Zorn, Ludwig; Ince, Stuart; Thierauch, Karl-Heinz; Menrad, Andreas; Haberey, Martin; Hess-Stumpp, Holger (Schering AG, Germany). Ger. Offen. DE 10228090 A1 20040115, 18 pp. (German). CODEN: GWXXBX. APPLICATION: DE 2002-10228090 20020619.
GI For diagram(s), see printed CA Issue.
AB Title compds. [I; R1 = (substituted) indazolyl, indolinyl, quinolinyl, Q1; R2 = H, C1-3 alkyl], were prepared Thus, 2-amino-N-(2-oxo-2,3-dihydro-1N-indol-6-yl)benzamide and pyridin-2-one-5-carboxaldehyde in MeOH was treated with ice AcOH followed by stirring over night at room temperature to give 82% N-(2-oxo-2,3-dihydro-1H-indol-6-yl)-2-[(6-oxo-1,6-dihydropyridin-3-yl)methylamino]benzamide. The latter inhibited VEGFR-2 (KDR) with IC50 = 0,05 μM.

L10 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2003:696673 Document No. 139:207829 Methods of extending corneal graft survival using **VEGFR-3 inhibitors** which inhibit lymphangiogenesis. De Vries, Gerald W. (Allergan, Inc., USA). PCT Int. Appl. WO 2003072029 A2 20030904, 84 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM,

to the patient an effective amount of a pharmaceutical composition vascular endothelial growth factor receptor-3 (**VEGFR-3**) **inhibitor**, whereby lymphangiogenesis is suppressed in the cornea of the patient. More specifically, the **VEGFR-3** **inhibitor** is a dominant neg. VEGFR-3 receptor, a nucleic acid encoding a dominant neg. VEGFR-3 receptor, a VEGFR-3 kinase inhibitor, an ATP analog, a VEGFR-3 binding mol., or a sequence-specific RNase.

L10 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2003:780133 Document No. 140:174592 CEP-7055: a novel, orally active pan inhibitor of vascular endothelial growth factor receptor tyrosine kinases with potent antiangiogenic activity and antitumor efficacy in preclinical models. Ruggeri, Bruce; Singh, Jasbir; Gingrich, Diane; Angeles, Thelma; Albom, Mark; Chang, Hong; Robinson, Candy; Hunter, Kathryn; Dobrzanski, Pawel; Jones-Bolin, Susan; Aimone, Lisa; Klein-Szanto, Andres; Herbert, Jean-Marc; Bono, Francoise; Schaeffer, Paul; Casellas, Pierre; Bourie, Bernard; Pili, Roberto; Isaacs, John; Ator, Mark; Hudkins, Robert; Vaught, Jeffry; Mallamo, John; Dionne, Craig (Department of Oncology, Cephalon, Inc., West Chester, PA, 19380, USA). Cancer Research, 63(18), 5978-5991 (English) 2003. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB Inhibition of the vascular endothelial growth factor VEGF-VEGF receptor (VEGF-R) kinase axes in the tumor angiogenic cascade is a promising therapeutic strategy in oncol. CEP-7055 is the fully synthetic orally active N,N-di-Me glycine ester of CEP-5214, a C3-(isopropylmethoxy) fused pyrrolocarbazole with potent pan-VEGF-R kinase inhibitory activity. CEP-5214 demonstrates IC50 values of 18 nM, 12 nM, and 17 nM against human VEGF-R2/KDR kinase, VEGF-R1/FLT-1 kinase, and VEGF-R3/FLT-4 kinase, resp., in biochem. kinase assays. CEP-5214 inhibited VEGF-stimulated VEGF-R2/KDR autophosphorylation in human umbilical vein endothelial cells (HUVECs) with an IC 50 of .apprx.10 nM and demonstrated an equivalent inhibition of murine FLK-1 autophosphorylation in transformed SVR endothelial cells. Evaluation of the antiangiogenic activity of CEP-5214 revealed a dose-related inhibition of microvessel growth ex vivo in rat aortic ring explant cultures and in vitro on HUVEC capillary-tube formation on Matrigel at low nanomolar concns. The antiangiogenic activity of CEP-5214 in these bioassays was observed in the absence of apparent cytotoxicity. Single-dose p.o. or s.c. administration of CEP-7055 or CEP-5214 to CD-1 mice at 23.8 mg/kg/dose b.i.d. resulted in a reversible inhibition of VEGF-R2/FLK-1 phosphorylation in murine lung tissues. Administration p.o. of CEP-7055 at 2.57 to 23.8 mg/kg/dose b.i.d. resulted in dose-related redns. in neovascularization in vivo in porcine aortic endothelial cell (PAEC)-VEGF/basic fibroblast growth factor-Matrigel implants in nude mice (maximum, 82% inhibition), significant redns. in granuloma formation (30%) and granuloma vascularity (42%) in a murine chronic inflammation-induced angiogenesis model, and significant and sustained (6 h) inhibition of VEGF-induced plasma extravasation in rats, with an ED50 of 20 mg/kg/dose. Chronic p.o. administration of CEP-7055 at doses of 11.9 to 23.8 mg/kg/dose b.i.d. resulted in significant inhibition (50-90% maximum inhibition relative to controls) in the growth of a variety of established murine and human s.c. tumor xenografts in nude mice, including A375 melanomas, U251MG and U87MG glioblastomas, CALU-6 lung carcinoma, ASPC-1 pancreatic carcinoma, HT-29 and HCT-116 colon carcinomas, MCF-7 breast carcinomas, and SVR angiosarcomas. Significant antitumor efficacy was observed similarly against orthotopically implanted LNCaP human prostate carcinomas in male nude mice and orthotopically implanted renal carcinoma (RENCA) tumors in BALB/c mice, in terms of a significant reduction in the

model) and reversible on withdrawal of treatment. Chronic p... administration of CEP-7055 in preclin. efficacy studies for periods of up to 65 days was well tolerated with no apparent toxicity or significant morbidity. Orally administered CEP-7055 has entered Phase I clin. trials in cancer patients.

L10 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2002:868928 Document No. 137:352900 Selective anthranilamide pyridine amides as inhibitors of VEGFR-2 and VEGFR-3. Ernst, Alexander; Huth, Andreas; Krueger, Martin; Thierauch, Karl-Heinz; Menrad, Andreas; Haberey, Martin (Schering Aktiengesellschaft, Germany). PCT Int. Appl. WO 2002090352 A2 20021114, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2002-EP4924 20020503. PRIORITY: DE 2001-10123574 20010508; DE 2001-10125294 20010515; DE 2001-10164590 20011221.
GI For diagram(s), see printed CA Issue.
AB Title compds. I [G, L, M, Q = N, (un)substituted CH, ≤1 of them being N; R = (un)substituted N heterocycle; R1 = (un)substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl] were prepared I are inhibitors of VEGFR-2 and VEGFR-3 and are used as medicaments for treating diseases that are caused by persistent angiogenesis, such as psoriasis, Kaposi's sarcoma, restenosis, such as e.g. stent-induced restenosis, endometriosis, Crohn's disease, Hodgkin's disease, leukemia, arthritis, such as rheumatoid arthritis, hemangioma, angiofibromatosis, in eye diseases such as diabetic retinopathy, neovascular glaucoma, in kidney diseases such as glomerulonephritis, diabetic nephropathy, malign nephrosclerosis, thrombic micro-angiopathic syndrome, transplant rejection and glomerulopathy, in fibrotic diseases such as hepatic cirrhosis, mesangial-cell proliferative diseases, arteriosclerosis, damage to the nerve tissue and inhibition of the re-occlusion of vessels after balloon catheter treatment, in vessel prosthetics or after the use of mech. devices for keeping vessels open, e.g. stents, as immunosuppressants, to support wound healing without scars and in cases of age spots and contact dermatitis. I can also be used as inhibitors of VEGFR-3 in lymphangiogenesis for hyperplastic and dysplastic changes in the lymphatic system. Thus, 2-amino-N-isoquinolin-3-ylbenzamide was treated with 2-bromo-5-pyridinecarboxaldehyde, followed by carboxylaton and amidation to give the amide II. II had IC50 for inhibition of VEGFR-2 of 40 nM and for inhibition of cytochrome 450 isoenzyme 2C9 of 2.9 μM.

L10 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2002:868925 Document No. 137:352899 Pyridylmethylanthranilamide N-oxides as inhibitors of VEGFR II kinase. Ernst, Alexander; Huth, Andreas; Krueger, Martin; Thierauch, Karl-Heinz; Menrad, Andreas; Haberey, Martin (Schering Aktiengesellschaft, Germany). PCT Int. Appl. WO 2002090349 A1 20021114, 50 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF,

NH; W = O, S, N2, (un)substituted NH, ..., = ... = (un)substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl; R2 = (un)substituted hetaryl N-oxide; R3 = H, alkyl] were prepared These compds. can be used in the treatment of psoriasis, Kaposi's sarcoma, restenosis, endometriosis, Crohn's disease, Hodgkin's disease, leukemia, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndromes, transplant rejections and glomerulopathy, fibrotic diseases such as cirrhosis of the liver, mesangial cell-proliferative diseases, arteriosclerosis, injuries of the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, for use in vascular prosthetics or after inserting mech. devices for holding vessels open such as, e.g. stents, as immunosuppressants, as an aid in scar-free wound healing, and for treating age spots and contact dermatitis. They can also be used as **VEGFR-3 inhibitors** in lymphangiogenesis. Thus, the N-oxide II was obtained by reductive alkylation of 2-amino-N-isoquinolin-3-ylbenzamide with isonicotinaldehyde N-oxide and had IC50 for inhibition of VEGFR II of 0.03 μM.

L10 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2002:793426 Document No. 137:310925 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt; Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M. (Abbott G.m.b.H. & Co. K.-G., Germany). PCT Int. Appl. WO 2002080926 A1 20021017, 867 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US9104 20020322. PRIORITY: US 2001-815310 20010322.
GI For diagram(s), see printed CA Issue.
AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or C6H4-4-CH2E; E = (un)substituted alkyl-OR, alkyl-CO2R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR2; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts., optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh3)4, and Na2CO3 in H2O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the benzaldehyde in the presence of Na(AcO)3BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of ≤ 50 μM. Certain compds. of the invention also significantly inhibited cdc2 or cellular

2002:555522 Document No. [illegible]
inhibitor materials and methods. Alitalo, Kari; Koivunen, Erkki; Kubo, Hajime (Ludwig Institute for Cancer Research, USA; Licentia Ltd.). PCT Int. Appl. WO 2002057299 A2 20020725, 149 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-IB99 20020116. PRIORITY: US 2001-PV262476 20010117.

AB The present invention relates to the diagnostics, evaluation, and therapeutic intervention of disorders mediated by the activity of cell surface receptor VEGFR-3, which activity often is stimulated by VEGFR-3 ligands VEGF-C and VEGF-D. More particularly, the present invention identifies novel methods and compns. for the inhibition of VEGF-C/D binding to VEGFR-3. The compns. of the present invention will be useful the inhibition of angiogenesis and lymphangiogenesis. Many uses of such compds., for screening samples, imaging, diagnosis, and therapy, are also provided. For example, in one emobiment, the invention provides an isolated peptide comprising the formula: X1X2X3X4X5X6X7X8, wherein X1 through X8 are amino acid residues.

L10 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN

2002:814851 Document No. 137:310930 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt; Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M. (Abbott Laboratories, USA). U.S. Pat. Appl. Publ. US 2002156081 A1 20021024, 426 pp., Cont.-in-part of U.S. Ser. No. 663,780. (English). CODEN: USXXCO. APPLICATION: US 2001-815310 20010322. PRIORITY: US 1999-PV154620 19990917; US 2000-663780 20000915.

GI For diagram(s), see printed CA Issue.

AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or C6H4-4-CH2E; E = (un)substituted alkyl-OR, alkyl-CO2R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR2; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts., optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh3)4, and Na2CO3 in H2O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the benzaldehyde in the presence of Na(AcO)3BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of ≤ 50 μM. Certain compds. of the invention also significantly inhibited cdc2 or cellular VEGF-induced KDR tyrosine kinase phosphorylation at concns. of ≤ 50 μM. Thus, I are useful for the treatment of a wide variety of disease states ameliorated by the inhibition of protein tyrosine kinase activity

Andreas; Haberey, Martin (Schering AG, Germany).
A1 20021121, 14 pp. (German). CODEN: GWXXBX. APPLICATION: DE 2001-10125295 20010515.

GI For diagram(s), see printed CA Issue.

AB Title compds. [I; A = NR7; W = O, S, 2H, NR8; Z = bond, NR10, :N, (branched) (substituted) alkyl; X = alkyl; R1 = (substituted) (branched) alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl; Y1-Y5 = N, CY6; Y6 = cyano, halo, alkyl, alkoxy, amino, OH (with the proviso that the ring contains at least one of N and is substituted with at least one of cyano group); D = N, CR3; E = N, CR4; F = N, CR5; G = N, CR6; R3-R6 = H, halo, (substituted) alkoxy, alkyl, carboxyalkyl; R7 = H, alkyl, etc.; R8-R10 = H, alkyl], were prepared Thus, N-(isoquinolin-3-yl)-2-(4-pyridylmethyl)aminobenzoic acid amide N-oxide was treated one after another with DMF, Et3N, and Me3SiCN followed by heating the bath temperature at 110° to give 14% N-(isoquinolin-3-yl)-2-[4-(2-cyanopyridyl)methyl]aminobenzoic acid amide. The latter inhibited the tyrosine kinase receptor VEGFR II (KDR) with IC50 = 1+10-8 mM.

L10 ANSWER 10 OF 11 MEDLINE on STN DUPLICATE 1

2002727866. PubMed ID: 12491250. Natural product derived receptor tyrosine kinase inhibitors: identification of IGF1R, Tie-2, and **VEGFR-3 inhibitors**. Stahl Petra; Kissau Lars; Mazitschek Ralph; Giannis Athanassios; Waldmann Herbert. (Max-Planck-Institut fur molekulare Physiologie, Abteilung Chemische Biologie, Otto-Hahn-Strasse 11, 44227 Dortmund, Germany.) Angewandte Chemie (International ed. in English), (2002 Apr 2) 41 (7) 1174-8. Ref: 27. Journal code: 0370543. ISSN: 0570-0833. Pub. country: Germany: Germany, Federal Republic of. Language: English.

L10 ANSWER 11 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2002:305612 The Genuine Article (R) Number: 538JM. Natural product derived receptor tyrosine kinase inhibitors: Identification of IGF1R, Tie-2, and **VEGFR-3 inhibitors**. Stahl P; Kissau L; Mazitschek R; Giannis A (Reprint); Waldmann H. Max Planck Inst Mol Physiol, Abt Chem Biol, Otto Hahn Str 11, D-44227 Dortmund, Germany (Reprint); Max Planck Inst Mol Physiol, Abt Chem Biol, D-44227 Dortmund, Germany; Univ Dortmund, Fachbereich Organ Chem 3, D-44221 Dortmund, Germany; Univ Karlsruhe, Inst Organ Chem, D-76128 Karlsruhe, Germany. ANGEWANDTE CHEMIE-INTERNATIONAL EDITION (1 APR 2002) Vol. 41, No. 7, pp. 1174-+. Publisher: WILEY-V C H VERLAG GMBH. PO BOX 10 11 61, D-69451 WEINHEIM, GERMANY. ISSN: 1433-7851. Pub. country: Germany. Language: English.

=> s keratoplasty
L11 17641 KERATOPLASTY

=> s l11 and rat
L12 357 L11 AND RAT

=> s l12 and corneal graft
L13 148 L12 AND CORNEAL GRAFT

=> s l13 transplantation
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=> s l14 and graft rejection
L16          90 L14 AND GRAFT REJECTION

=> s l16 and inhibitor
L17           0 L16 AND INHIBITOR

=> dup remove l16
PROCESSING COMPLETED FOR L16
L18          55 DUP REMOVE L16 (35 DUPLICATES REMOVED)

=> s l18 and "VEGFR"
L19           0 L18 AND "VEGFR"

=> s l18 and survival
L20          32 L18 AND SURVIVAL

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PROCESSING COMPLETED FOR L20
L21          32 DUP REMOVE L20 (0 DUPLICATES REMOVED)

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L21  ANSWER 1 OF 32  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
2004104195  EMBASE  An experimental study on the correlation of penetrating
     keratoplasty reject and cornea preservation methods. Shi J.; Gu
     S.. J. Shi, Department of Ophthalmology, Affiliated Third Hospital, Jilin
     University, Changchun 130021, China. Chinese Ophthalmic Research  22/1
     (9-12)  2004.
     Refs: 9.
     ISSN: 1003-0808. CODEN: YAYAFH. Pub. Country: China. Language: Chinese.
     Summary Language: English; Chinese.
AB   Objective: To understand the relation between the penetrating
     keratoplasty reject and the time of preserved cornea. Methods: The
     30 Wistar rats and 15 SD rats were used to establish
     the animal models of penetrating keratoplasty reject and were
     randomly divided into 3 groups. The different time preservated cornea
     donor of SD rats were used separately in three groups. The other
     15 Wistar rats and 15 SD rats were randomly divided
     into 3 groups as control. The penetrating keratoplasty rejection
     index (RI) in postoperation, means survival time (MST) of
     corneal grafts and histopathological changes were
     analyzed. Results: The MST was 8.11±0.93 days in short-term-preserved
     group, 12.57±0.98 days in medium-term-preserved group and 9.63±0.747
     days in long-term-preserved group. The MST in medium-term-preserved group
     was evidently prolonged, showing a significant correlation among three
     groups (P<0.01). Conclusion: The rate of rejection of penetrating
     keratoplasty in postoperation was decreased and rejection time was
     delayed in medium-term-preserved cornea.

L21  ANSWER 2 OF 32     MEDLINE on STN
2003350954.    PubMed ID: 12882780.   Rat corneal allograft
     survival prolonged by the superantigen staphylococcal enterotoxin
     B. Pan Zhiqiang; Chen Yu; Zhang Wenhua; Jie Ying; Li Na; Wu Yuying.
     (Beijing Institute of Ophthalmology, Beijing TongRen Eye Center, Capital
     University of Medical Sciences, Beijing, China.. ebank416@msn.com) .
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rat model of penetrating **keratoplasty**, whereby [illegible] donor corneas are implanted into Lewis recipients, was used to evaluate the effects of SEB on inhibiting immune-mediated allograft rejection. To induce anergy, SEB was injected into the peribulbar space of Lewis **rats**. Furthermore, histopathology and immunofluorescent staining were used to examine the levels of infiltrating CD4(+) and CD8(+) T lymphocytes and NK1.1(+) lymphocytes. RESULTS: By administering SEB, at doses of 90 or 120 micro g/kg 7 days before and after **keratoplasty**, we suppressed the episode of **corneal graft rejection** for a median of 12 and 30 days, respectively. In contrast, rejection was observed when 30 or 60 micro g/kg of SEB was administered. After SEB injections, lymphocyte infiltration into the **corneal grafts** was reduced, and the expression of NK1.1(+) lymphocytes was enhanced, suggesting that anergy may be occurring. Also, there were no differences in the number of infiltrating CD4(+) and CD8(+) T lymphocytes cells between the control group and groups injected with 30 and 120 micro g/kg SEB on postoperative days 10 and 30. CONCLUSIONS: Inducing anergy with the superantigen SEB prolonged **corneal graft survival** in a **rat** model of penetrating **keratoplasty**. Therefore, these results support the possibility of prolonging corneal allograft **survival** in a clinical setting by preventing immune-mediated rejection through the administration of the superantigen SEB.

L21 ANSWER 3 OF 32 MEDLINE on STN

2004066472. PubMed ID: 14766071. Effects of IL-1 receptor antagonist on the level of cytokine in the **rat corneal grafts** and aqueous humor after corneal **transplantation**.

Zhang Wen-hua; Zhai Chang-bin; Pan Zhi-qiang; Wu Yu-ying. (Beijing Institute of Ophthalmology, Beijing Tongren Ophthalmic Center, Capital University of Medical Science, Beijing 100730, China.. panxiaow@public3.bta.net.cn) . [Zhonghua yan ke za zhi] Chinese journal of ophthalmology, (2003 Oct) 39 (10) 587-91. Journal code: 16210540R. ISSN: 0412-4081. Pub. country: China. Language: Chinese.

AB OBJECTIVE: By detecting the expression of IL-1RI and TGF-beta(1) on the normal **rat** cornea and graft, and the amount of IL-1 beta in the aqueous humor of normal **rat** eye and the eye after **keratoplasty**, to investigate the relationship between these cytokines and **graft rejection** and to observe the effects of IL-1 receptor antagonist (IL-1ra) on **graft rejection**. METHODS: All **rats** after **keratoplasty** were divided into five groups. Immunohistochemistry method and enzyme-linked immunosorbent assay (ELISA) were used to detect the expression of IL-1RI and TGF-beta(1) on the normal **rat** cornea and graft and the amount of IL- 1 beta in the aqueous humor of normal **rat** eye and the eye after **keratoplasty** at different time points: pre-rejection, acute-rejection and two weeks after surgery. RESULTS: IL-1RI could be detected in normal **rat** cornea. TGF-beta(1) expressed mainly in the epithelium of normal cornea, especially the basal cell layer and the basement membrane. After **keratoplasty**, IL-1RI and TGF-beta(1) could be detected in the corneal epithelium, stroma and endothelium, and the level of expression decreased in sequence as negative control group, 50 micro g IL-1ra group, 100 micro g IL-1ra group, 200 micro g IL-1ra group and dexamethasone group. In the acute rejection period, the expression of IL-1RI and TGF-beta(1) in the 200 micro g IL-1ra group was less than that of the 50 micro g IL-1ra group, the difference was significant ($P < 0.01$). The

quantity of IL-1 beta reached its peak at (...) negative control group, which was the highest quantity of IL-1 beta in all experimental groups ($P < 0.01$). The IL-1 beta level in all experimental groups in the pre-rejection period had no difference compared with that in the acute rejection period ($P > 0.05$), but the level of IL-1 beta in the pre-rejection and rejection periods was significantly different compared with that in the post-rejection period ($P < 0.01$). CONCLUSIONS: IL-1RI and TGF-beta(1) play a active role in the **corneal graft** immunogenic rejection. IL-1 beta is a key factor in starting **corneal graft rejection**. The **keratoplasty** graft rejecting reaction can be reduced and mean **survival** time can be prolonged by IL-1ra, which inhibits the expression of IL-1RI and TGF-beta(1) and decreases the level of IL-1 beta in the aqueous humor.

L21 ANSWER 4 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:393548 The Genuine Article (R) Number: 673XF. Effect of topical dexamethasone treatment on antigen-presenting cells in murine corneas. Muller A (Reprint); Zhang E P; Hoffmann F. Free Univ Berlin, Klinikum Benjamin Franklin, Augenklin, Hindenburgdamm 30, D-12200 Berlin, Germany (Reprint); Free Univ Berlin, Klinikum Benjamin Franklin, Augenklin, D-12200 Berlin, Germany. OPHTHALMOLOGE (APR 2003) Vol. 100, No. 4, pp. 310-313. Publisher: SPRINGER-VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010 USA . ISSN: 0941-293X. Pub. country: Germany. Language: German.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective. To determine the influence of dexamethasone treatment on APCs and the time of graft **survival** of MHC-disparate grafts.

Methods. Flatmounts of the ocular surface prepared with EDTA and tangential frozen sections of the remaining corneal stroma from untreated eyes of normal mice (n=6) and from eyes treated for 7 days with dexamethasone (n=6) were immunohistologically examined for content of F4/80+ and MHC II+ cells. Furthermore, corneas of C3H mice without and with 7-day dexamethasone eye drop treatment (n=8) were grafted into BALB/c mice receiving the same treatment.

Results. The number of positive cells within the epithelial flatmounts showed a dramatic reduction in the dexamethasone-pretreated group ($p<0.01$ compared to the untreated control group). The number of positive cells in the corneal stroma remained unchanged. The grafts of untreated control mice survived 16 4 clays,the treated grafts 16 3 days.

Conclusions. Most investigators assume that normal murine corneas contain no APCs such as macrophages and Langerhans cells. For the first time we were able to detect APCs in flatmounts of the ocular surface and frozen sections of corneal stroma. Our investigations show that, in contrast to the ocular surface, the number of F4/80+ cells in the corneal stroma is not influenced by dexamethasone treatment. **Transplantation** of corneas containing donor-derived APCs promotes acute rejection (direct pathway of allorecognition). Thus, dexamethasone treatment did not prolong the time of allograft **survival**.

L21 ANSWER 5 OF 32 MEDLINE on STN
2002162817. PubMed ID: 11862095. Intraocular dexamethasone delivery system for corneal **transplantation** in an animal model. Kagaya Fumie; Usui Tomohiko; Kamiya Kazutaka; Ishii Yasuo; Tanaka Sumiyoshi; Amano Shiro; Oshika Tetsuro. (Department of Ophthalmology, University of Tokyo School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113 8655, Japan.) Cornea, (2002 Mar) 21 (2) 200-2. Journal code: 8216186. ISSN: 0277-3740. Pub. country: United States. Language: English.

betamethasone eyedrops three times daily for 8 weeks, and [illegible]
DEX DDS in the anterior chamber at the time of **transplantation**. RESULTS: All grafts in the untreated control group were rejected within 8 days. In the betamethasone eyedrop group, five eyes (83%) were rejected during the 8-week study period. None of the grafts in the DEX DDS group was rejected. The administration of DEX DDS significantly prolonged the **survival** rate of the **corneal grafts** ($p < 0.001$, log-rank test). CONCLUSION: DEX DDS is effective in suppressing **graft rejection** in high-risk corneal **transplantation**.

L21 ANSWER 6 OF 32 MEDLINE on STN

2002197598. PubMed ID: 11930640. Effect of a cyclosporine A delivery system in corneal **transplantation**. Xie Lixin; Shi Weiyun; Wang Zhiyu; Bei Jianzhong; Wang Shenguo. (Shandong Eye Institute, Qingdao 266071, China.. lixinxie@public.qd.sd.cn) . Chinese medical journal, (2002 Jan) 115 (1) 110-3. Journal code: 7513795. ISSN: 0366-6999. Pub. country: China. Language: English.

AB OBJECTIVE: To test the immunosuppressive effect of cyclosporine (Cs) in a polymer placed in the anterior chamber of corneal allograft recipients. METHODS: Wistar inbred **rats** with vascularized corneas were recipients of corneal allografts from Sprague-Dawley donor **rats**. **Rats** underwent penetrating **keratoplasty** and were divided randomly into four groups: untreated control animals (UCA); Cs-polymer anterior chamber recipients (CPA); co-polymer subconjunctival recipients (CPS); and Cs-olive oil drop recipients (COO). Grafts were examined by slit lamp every 3 days and clinical conditions were scored. Cs concentration in the aqueous humor was assayed at 1, 2, and 4 weeks. At 1, 2 and 4 weeks after **transplantation**, the operated eyes were collected for histopathological evaluation of the grafts. RESULTS: The median **survival** time of the allografts was 8.2 +/- 1.48 days for the UCA group, 11.4 +/- 2.50 days for the CPS group, and 17.0 +/- 2.00 days for the CPA group. There was a statistically significant difference ($P < 0.05$) between **survival** time of the allografts in the animals of the CPA group compared to the other groups of graft recipients. Significantly higher concentrations of Cs were found in the eyes given an anterior chamber implant of Cs-polymer, compared to other treatment groups or untreated **rats**. A transient inflammatory response in the anterior chamber was observed in the CPA group. CONCLUSIONS: Cs-polymer placed in the anterior chamber significantly prolongs corneal allograft **survival** time in a high risk **corneal graft rejection** model. This intraocular delivery system may be a valuable adjunct for the suppression of immune **graft rejection**.

L21 ANSWER 7 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2002:65728 The Genuine Article (R) Number: 509ZM. Evaluation of **corneal graft rejection** in a mouse model. Plskova J; Kuffova L; Holan V; Filipec M; Forrester J V (Reprint). Univ Aberdeen, Dept Ophthalmol, Polwarth Bldg, Aberdeen AB25 2ZD, Hong Kong, Peoples R China (Reprint); Univ Aberdeen, Dept Ophthalmol, Aberdeen AB25 2ZD, Hong Kong, Peoples R China. BRITISH JOURNAL OF OPHTHALMOLOGY (JAN 2002) Vol. 86, No. 1, pp. 108-113. Publisher: BRITISH MED JOURNAL PUBL GROUP. BRITISH MED ASSOC HOUSE, TAVISTOCK SQUARE, LONDON WC1H 9JR, ENGLAND . ISSN: 0007-1161. Pub. country: Peoples R China. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB **Corneal graft rejection** presents

previous experimental studies of allograft rejection [illegible] are reviewed to support the latter mechanism.

L21 ANSWER 8 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:524237 The Genuine Article (R) Number: 563XU. Efficacy and safety of microspheres of cyclosporin A, a new systemic formulation, to prevent **corneal graft rejection** in **rats**.
Vallelado A I (Reprint); Lopez M I; Calonge M; Sanchez A; Alonso M J. Univ Valladolid, Inst Univ Oftalmobiol Aplicada, Ramon & Cajal 7, E-47005 Valladolid, Spain (Reprint); Univ Valladolid, Inst Univ Oftalmobiol Aplicada, E-47005 Valladolid, Spain; Univ Santiago de Compostela, Dept Pharmaceut Technol, Santiago De Compostela, Spain. CURRENT EYE RESEARCH (12 JUN 2002) Vol. 24, No. 1, pp. 39-45. Publisher: SWETS ZEITLINGER PUBLISHERS. P O BOX 825, 2160 SZ LISSE, NETHERLANDS. ISSN: 0271-3683. Pub. country: Spain. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Purpose. To evaluate the efficacy and safety of a new systemic formulation of cyclosporin A (CsA)-loaded microspheres in a **rat** model of penetrating **keratoplasty** rejection.
Methods. Female Lewis **rats** received orthotopic corneal allografts from inbred female Fisher donors. The **rats** were divided into three groups: 1, untreated controls; 2, daily subcutaneous injection of 10 mg/kg of the commercially intravenous CsA formulation starting after surgery (time 0) and for 15 days; and 3, one subcutaneous injection of 150 mg/kg of CsA microspheres. The grafts were evaluated clinically for 30 days and the rejection index, mean **survival** time, and rejection rate were calculated. Serum levels of CsA were measured at 5, 10, 15, 20, and 30 days in groups 2 and 3. Eyes, liver, and kidneys were histologically evaluated at the end of the experiment.
Results. **Graft rejection** was significantly reduced in group 3 at day 30 ($P < 0.05$) and serum levels of CsA were constant (range, 73.28 &PLUSMN; 43.93 to 183.33 &PLUSMN; 83.69 ng/ml). High levels (3000 ng/ml) were obtained in group 2 as long as CsA was injected. Both formulations delayed rejection onset, but only the microspheres decreased the rate of **corneal graft rejection** (100% in group 2 and 70% in group 3 at day 30). Histologic examination showed no hepatic lesions with either formulation, but both resulted in deposition of a hemoglobin-like material in the kidneys.
Conclusions. Although subcutaneous CsA-loaded microspheres delay rejection onset and decrease the rate of **corneal graft rejection** in an orthotopic **keratoplasty** rejection model in **rats**, administration of the microspheres did not prevent acute renal toxicity.

L21 ANSWER 9 OF 32 MEDLINE on STN
2001540191. PubMed ID: 11588429. Prolongation of corneal allograft **survival** using cyclosporine in a polylactide-co-glycolide polymer.
Xie L; Shi W; Wang Z; Bei J; Wang S. (Shandong Eye Institute and Hospital, 5 Yanerdao Road, Qingdao 266071, China.. lixinxie@public.qd.sd.cn) .
Cornea, (2001 Oct) 20 (7) 748-52. Journal code: 8216186. ISSN: 0277-3740. Pub. country: United States. Language: English.
AB PURPOSE: To test for prolongation of corneal transplant **survival** with cyclosporine in a polymer placed in the anterior chamber of corneal allograft recipients. METHODS: Wistar inbred **rats** with vascularized corneas were recipients of corneal allografts from Sprague-Dawley donor **rats**. Grafted **rats** were randomized into six groups: untreated control animals,

transplantation, the eyes were collected for histopathology evaluation of the grafts. RESULTS: The median **survival** time of untreated corneal allografts was 8.2 +/- 1.48 days for grafts treated with topical cyclosporine, 8.5 +/- 1.50 days for polymer-only anterior chamber implants, 10.6 +/- 1.90 days for 1% cyclosporine drops, 11.4 +/- 2.50 days for grafts given subconjunctival cyclosporine-polymer, 17 +/- 3.05 days for grafts given cyclosporine-polymer implants in the anterior chamber, and more than 3 months in autografted **rats**. There was a statistically significant difference ($p < 0.05$) between the **survival** time of the allografts in the animals treated with the cyclosporine-polymer in the anterior chamber compared with the other groups of graft recipients. Significantly higher concentrations of cyclosporine were found in the eyes given an anterior chamber implant of cyclosporine-polymer than in the other treatment groups or the untreated **rats**. The cyclosporine-polymer implants placed in the anterior chamber induced a transient inflammatory response in transplanted eyes. CONCLUSIONS: Cyclosporine-polymer placed in the anterior chamber significantly prolongs corneal allograft **survival** in a high-risk **corneal graft rejection**. This intraocular delivery system may be a valuable adjunct for the suppression of immune **graft rejection** in high-risk recipients of corneal transplants.

L21 ANSWER 10 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:914683 The Genuine Article (R) Number: 493KG. Mechanisms of **corneal graft rejection** - The Sixth Annual Thygeson Lecture, Presented at the Ocular Microbiology and Immunology Group Meeting, October 21, 2000. Niederkorn J Y (Reprint). Univ Texas, SW Med Ctr, Dept Ophthalmol, 5323 Harry Hines Blvd, Dallas, TX 75235 USA (Reprint); Univ Texas, SW Med Ctr, Dept Ophthalmol, Dallas, TX 75235 USA. CORNEA (OCT 2001) Vol. 20, No. 7, pp. 675-679. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 0277-3740. Pub. country: USA. Language: English.

L21 ANSWER 11 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:508263 The Genuine Article (R) Number: 442MF. Corneal allograft rejection: Current understanding I. Immunobiology and basic mechanisms. Pleyer U (Reprint); Dannowski H; Volk H D; Ritter T. Humboldt Univ, Dept Ophthalmol, Charite, Augustenburger Pl 1, D-13353 Berlin, Germany (Reprint); Humboldt Univ, Dept Ophthalmol, Charite, D-13353 Berlin, Germany; Humboldt Univ, Inst Med Immunol, Charite, D-13353 Berlin, Germany . OPHTHALMOLOGICA (JUL-AUG 2001) Vol. 215, No. 4, pp. 254-262. Publisher: KARGER. ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 0030-3755 . Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Allograft rejection remains the single largest impediment to success in corneal **transplantation**. This article briefly reviews our current understanding of some fundamental aspects of corneal immunology and the pathogenetic mechanisms underlying **corneal graft rejection**. As knowledge increases, it is hoped that a better understanding of the immunobiology may result in improved preventive and therapeutic measures. Copyright (C) 2001 S.KargerAG. Basel.

L21 ANSWER 12 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:318995 The Genuine Article (R) Number: 421KL. The effect of duration and timing of systemic cyclosporine therapy on corneal allograft **survival** in a **rat** model. Claerhout I (Reprint); Beele

OPHTHALMOLOGY (FEB 2001) Vol. 239, No. 2, pp. [illegible]
SPRINGER-VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010 USA. ISSN: 0721-832X.
Pub. country: Belgium. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Systemic cyclosporine A (CsA) remains a valuable treatment option in the prevention of **corneal graft rejection**, but the question of timing and duration of this systemic therapy remains unresolved. The effect of a pre- and postoperative dosing schedule, related to the expected moment of rejection, was examined in a **rat** model. Methods: All A0 (strain) recipients of PVG grafts were assigned to the following treatment groups: Group 1 (controls), groups 2-5 (a postoperative treatment regimen of CsA for 5, 10, 15 and 30 days respectively) and groups 6 and 7 (CsA preoperatively for 5 days and postoperatively for another 5 or 10 days respectively). Corneal allografts were clinically evaluated and blood CsA levels were measured at various time points. Results: Untreated controls rejected their allografts after 13 days. Regression analysis showed a strongly significant positive correlation between graft **survival** time and duration of cyclosporine therapy. There was no difference in graft **survival** between groups 3 (CsA 10 days) and 4 (CsA 15 days). A pre-operative dosing schedule of CsA followed by postoperative treatment had no advantage over a solely postoperative treatment regimen. The moment of rejection was characterized by a low to undetectable CsA concentration. Conclusion: The present study demonstrates a significant influence of the duration of systemic CsA administration on allograft **survival** time. However, preoperative administration of CsA does not seem to have an additional influence on graft **survival**, which is in line with the biological evidence of the mechanism of action of CsA on the efferent arm of **graft rejection**.

L21 ANSWER 13 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:750660 The Genuine Article (R) Number: 358PZ. The role of cytotoxic T lymphocytes in corneal allograft rejection. Hegde S; Niederkorn J Y (Reprint). UNIV TEXAS, SW MED CTR, DEPT OPHTHALMOL, 5323 HARRY HINES BLVD, DALLAS, TX 75390 (Reprint); UNIV TEXAS, SW MED CTR, DEPT OPHTHALMOL, DALLAS, TX 75390; UNIV TEXAS, SW MED CTR, GRAD PROGRAM IMMUNOL, DALLAS, TX 75390. INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (OCT 2000) Vol. 41, No. 11, pp. 3341-3347. Publisher: ASSOC RESEARCH VISION OPHTHALMOLOGY INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0146-0404. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB PURPOSE. Immunologic rejection constitutes a major barrier to the success of allogeneic corneal transplants, but the specific mediators and mechanisms of **graft rejection** are poorly understood. Several studies have implicated cytotoxic T-lymphocyte (CTL) responses, typically associated with CD8(+) T cells, in promoting **corneal graft rejection**. This study sought to test the hypothesis that CTLs are essential in promoting **corneal graft rejection**.

METHODS. BALB/c donor corneas were grafted orthotopically onto C57BL/6, perforin knockout, or CD8(+) T-cell knockout mice. The tempo and incidence of **graft rejection** were observed for each group. In separate experiments, donor-specific CTL and delayed-type hypersensitivity (DTH) responses were tested at the time of **graft rejection** by a standard chromium release assay and an ear swelling assay, respectively.

RESULTS. Perforin knockout and CD8(+) T-cell knockout mice were as

essential in promoting **corneal graft rejection**
and instead further implicates donor-specific DTH reactions as the relevant immune response during graft failure.

L21 ANSWER 14 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:548083 The Genuine Article (R) Number: 334VU. The effect of corticosteroid and cyclosporin A on murine corneal allograft rejection. Zhang E P; Schulte F; BulfonePaus S; Hoffmann F (Reprint). FREE UNIV BERLIN, KLINIKUM BENJAMIN FRANKLIN, AUGENKLIN & POLIKLIN, HINDENBURGDAMM 30, D-12200 BERLIN, GERMANY (Reprint); FREE UNIV BERLIN, KLINIKUM BENJAMIN FRANKLIN, AUGENKLIN & POLIKLIN, D-12200 BERLIN, GERMANY; FREE UNIV BERLIN, KLINIKUM BENJAMIN FRANKLIN, INST IMMUNOL, D-12200 BERLIN, GERMANY. GRAEFES ARCHIVE FOR CLINICAL AND EXPERIMENTAL OPHTHALMOLOGY (JUN 2000) Vol. 238, No. 6, pp. 525-530. Publisher: SPRINGER VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010. ISSN: 0721-832X. Pub. country: GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Background: The immunomodulatory T-helper type 1 (Th1) cytokine interferon-gamma (IFN-gamma) was measured in serum and cornea to ascertain its general contribution to **corneal graft rejection** and to establish a rational basis for the decision for or against systemic therapy.

Methods: Eight groups of differently treated BALB/c (H-2d) mice received a C3H (H-2 k) **corneal graft**. There was one saline-treated control group and two groups that received intramuscular cyclosporin A (CsA) for 14 or 40. Three groups received systemic or topical, systemic plus topical corticosteroid treatment, which was combined with CsA in two further groups. To measure the IFN-gamma level by enzyme-linked immunosorbent assay (ELISA), blood was taken by heart puncture and corneae were excised at the limbus. Results: Five days of systemic corticosteroid and 14 days of CsA had no significant effect on graft **survival**. A 40-day CsA treatment and a 40-day combined corticosteroid treatment significantly prolonged graft **survival**. An 80-day topical corticosteroid treatment produced additional prolongation. IFN-gamma could not be detected (limit of detection 25 pg/ml) in any of the serum samples, while significantly increased amounts of IFN-gamma were detected in the supernatants of the corneal tissue 13 or 14 days after allogeneic but not syngeneic **corneal graft**, corresponding to 9.5 pg, 5.1 pg and 1.8 pg per cornea.

Conclusion: The detection of Th1 cytokines in the cornea but not the serum of mice at the time of allograft rejection is in accordance with the finding of long-lasting dose-dependent immunosuppression of topical steroids and the inefficacy of shortterm systemic CsA and corticosteroids.

L21 ANSWER 15 OF 32 MEDLINE on STN
1999328181. PubMed ID: 10401754. The immune privilege of corneal allografts. Niederkorn J Y. (Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas 75235-9057, USA.) Transplantation, (1999 Jun 27) 67 (12) 1503-8. Ref: 55. Journal code: 0132144. ISSN: 0041-1337. Pub. country: United States. Language: English.
AB BACKGROUND: Corneal **transplantation** is the oldest, most common, and arguably, the most successful form of tissue **transplantation**. In the United States alone, over 40,000 corneal **transplantations** are performed each year. Less than 10% of the uncomplicated, first-time **corneal grafts** will undergo immune rejection even though HLA matching is not routinely performed and the use of immunosuppressive drugs is limited to the topical application of corticosteroids. The success of corneal **transplantations**

the conspicuous avascularity of the cornea, which has [illegible] sequester the graft from the immune apparatus. However, results from several laboratories indicate that at least three additional features of the **corneal graft** contribute to its immune privileged status: (a) absence of donor-derived, antigen-presenting passenger Langerhans cells in the **corneal graft**; (b) expression of Fas ligand on the epithelium and endothelium of the corneal allograft; and (c) capacity of the corneal allograft to induce immune deviation of the systemic immune response. CONCLUSIONS: The immune privilege of corneal allografts is a product of at least three unique qualities of the corneal allograft that conspire to interfere with the induction and expression of allodestructive immune responses.

L21 ANSWER 16 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:864390 The Genuine Article (R) Number: 253DT. Beneficial effect of preoperative mycophenolate mofetil in murine corneal **transplantation.** Reis A (Reprint); Spelsberg H; Reinhard T; Braunstein S; Godehardt E; Sundmacher R. UNIV DUSSELDORF, EYE CLIN, MOORENSTR 5, D-40225 DUSSELDORF, GERMANY (Reprint). TRANSPLANT INTERNATIONAL (OCT 1999) Vol. 12, No. 5, pp. 341-345. Publisher: SPRINGER VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010. ISSN: 0934-0874. Pub. country: GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB To investigate the effect of preoperative mycophenolate mofetil (MMF) on allograft **survival** in a murine corneal **transplantation** model. Corneal grafting was performed from Brown Norway to Lewis **rats**. Groups were divided as follows: **Rats** that received syngeneic or allogeneic grafts without therapy served as controls. MMF treatment was either started 7 days prior to **transplantation** and continued for 14 postoperative days (POD) or started at the day of corneal grafting until POD 14. MMF (20 mg/kg) administered postoperatively had no significant beneficial effect on **corneal graft survival** when compared with controls. However, the group receiving 40 mg/kg MMF postoperatively showed a statistically significant prolonged graft **survival**. A 1-week preoperative administration of 20 mg/kg MMF allowed superior graft **survival**. Priming the immune system of corneal transplant recipients preoperatively with MMF proved to be a beneficial therapeutic regimen for prolonging corneal allograft **survival** in **rats**.

L21 ANSWER 17 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:432330 The Genuine Article (R) Number: 201UJ. A new model of orthotopic penetrating corneal **transplantation** in the sheep: Graft **survival**, phenotypes of graft-infiltrating cells and local cytokine production. Williams K A (Reprint); Standfield S D; Mills R A D; Takano T; Larkin D F P; Krishnan R; Russ G R; Coster D J. FLINDERS MED CTR, DEPT OPHTHALMOL, BEDFORD PK, SA 5042, AUSTRALIA (Reprint); FLINDERS UNIV S AUSTRALIA, ADELAIDE, SA 5001, AUSTRALIA; QUEEN ELIZABETH HOSP, WOODVILLE, SA 5011, AUSTRALIA; JUNTENDO UNIV, TOKYO 113, JAPAN; MOORFIELDS EYE HOSP, LONDON, ENGLAND. AUSTRALIAN AND NEW ZEALAND JOURNAL OF OPHTHALMOLOGY (APR 1999) Vol. 27, No. 2, pp. 127-135. Publisher: ROYAL AUSTRALIAN COLL OPHTHAL. 27 COMMONWEALTH ST, SYDNEY NSW 2010, AUSTRALIA. ISSN: 0814-9763. Pub. country: AUSTRALIA; JAPAN; ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Background: Orthotopic penetrating **keratoplasty** in the sheep

specimens. Cytokine mRNA was detected by polymerase [illegible]
Results: Corneal autografts survived indefinitely. Allografts became vascularized and underwent rejection at a median of 20 days postgraft. Both endothelial and epithelial rejection lines were observed. Immunohistochemical staining of rejecting grafts showed up-regulation of major histocompatibility complex class I molecules on **corneal graft** epithelium, damaged or absent graft endothelium and a marked, pre-dominantly mononuclear cell infiltrate. CD4-positive T cells were observed in the graft within 2 days of the onset of rejection, followed several days later by CD8-positive T cells. Messenger RNA transcripts for interleukin (IL)-2, tumour necrosis factor (TNF)-alpha and IL-10 (but not for interferon (IFN)-gamma or IL-4) were found in autographed corneas. Proportionately, more allografts than autografts contained transcripts for IL-2 and TNF-alpha and IFN-gamma was detected in three of four allografts.
Conclusions: **Corneal graft rejection** in the sheep is macroscopically and histologically similar to human **corneal graft** CD-8 positive T cells and local production of pro-inflammatory cytokines occurs during **graft rejection**.

L21 ANSWER 18 OF 32 MEDLINE on STN
2002140620. PubMed ID: 11835769. Experimental studies on the effect of the immunosuppressant FK-506 on penetrating **keratoplasty** rejection model in **rats**. Lu L; Zhang W; Sun X. (Department of Ophthalmology, Affiliated Tong Ren Hospital, Capital Medical University, Beijing 100730.) [Zhonghua yan ke za zhi] Chinese journal of ophthalmology, (1999 Jan) 35 (1) 25-8. Journal code: 16210540R. ISSN: 0412-4081. Pub. country: China. Language: Chinese.
AB OBJECTIVE: To study the immunosuppressive effects of FK-506 on allogeneic **transplantation** in a **rat** model. METHODS: Inbred strain Lou **rats** were used as recipients, and F344 **rats** were used as donors. Subconjunctival injection of FK-506 0.1 mg/kg and cyclosporine A (CsA) 3 mg/kg were administered respectively for 2 weeks, and the grafts were inspected by clinical evaluation. RESULTS: The group receiving FK-506 had a significant delay in allograft rejection with mean **survival** time (22.1 +/- 5.17) days vs. (18.4 +/- 1.4) days for the CsA group and (12.1 +/- 2.13) days for the control group ($P < 0.01$). CONCLUSION: It is indicated that FK-506 would be a useful drug to suppress **corneal graft rejection**.

L21 ANSWER 19 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1998:477714 The Genuine Article (R) Number: ZU407. Effect of mycophenolate mofetil, cyclosporin A, and both in combination in a murine **corneal graft rejection** model. Reis A (Reprint); Reinhard T; Sundmacher R; Braunstein C; Godehardt E. HEINRICH HEINE UNIV, AUGENKLIN, MOORENSTR 5, D-40225 DUSSELDORF, GERMANY (Reprint); UNIV DUSSELDORF, DEPT PATHOL, D-4000 DUSSELDORF, GERMANY; UNIV DUSSELDORF, DEPT BIOMETRY, DEPT CARDIAC & THORAC SURG, D-4000 DUSSELDORF, GERMANY. BRITISH JOURNAL OF OPHTHALMOLOGY (JUN 1998) Vol. 82, No. 6, pp. 700-703. Publisher: BRITISH MED JOURNAL PUBL GROUP. BRITISH MED ASSOC HOUSE, TAVISTOCK SQUARE, LONDON WC1H 9JR, ENGLAND. ISSN: 0007-1161. Pub. country: GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Aims-To compare the effectiveness of mycophenolate mofetil (MMF), cyclosporin A (CSA), and both in combination, in preventing rejection following corneal **transplantations**.

subjected to histological or immunohistological evaluation.

Results-The average transplant **survival** rate in the allogenic strain combination was 7.9 days (SEM 1.1). Monotherapy with MMF led to a statistically significant prolongation of transplant **survival** to 11.6 days (SEM 0.9, p< 0.05). Monotherapy with CSA delayed transplant rejection statistically significantly longer than MMF (21 days, 0.0, p< 0.05). The combination therapy with CSA and MMF was statistically significantly superior to the monotherapy with MMF (22.3 days, 0.5, p< 0.05). The combination therapy prolonged transplant **survival** compared with the CSA monotherapy, albeit not to a statistically significant extent.

Conclusions-In this study we were able to prove the immunosuppressive effect of oral MMF on acute rejection following corneal **transplantation**. Double drug therapy with CSA and MMF conferred a marginal benefit without a higher incidence of complications related to drug toxicity or overimmunosuppression.

L21 ANSWER 20 OF 32 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

1998026420 EMBASE Efficacy of topical cyclosporine-loaded nanocapsules on **keratoplasty** rejection in the **rat**. Juberias J.R.; Calonge M.; Gomez S.; Lopez M.I.; Calvo P.; Herreras J.M.; Alonso M.J.. Dr. M. Calonge, IOBA, Facultad Medicina, Universidad de Valladolid, Ramon y Cajal 7, 47005 Valladolid, Spain. calonge@ioba.med.uva.es. Current Eye Research 17/1 (39-46) 1998.
Refs: 40.
ISSN: 0271-3683. CODEN: CEYRDM. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Purpose. To evaluate the efficacy of a topical formulation of nanocapsules loaded with 1% cyclosporine A (CsA), which has been previously demonstrated to enhance CsA corneal penetration, compared to 1% CsA in migliol oil on a penetrating **keratoplasty** rejection model in the **rat**. Methods. Lewis **rats** received orthotopic corneal allografts from inbred Fisher donors. **Rats** were treated with 10 μl of the following topical solutions four times daily for 30 days, starting one day before surgery: Group 1 (n = 9), 1% CsA-loaded nanocapsules: group 2 (n = 13), 1% CsA dissolved in migliol oil; group 3 (n = 12), migliol oil; group 4 (n = 13), no treatment. Rejection index, mean **survival** time and rejection percentage were calculated for each group, and CsA levels in blood were measured. Results. The rejection percentage was 84.6% for group 2, 91.7% for group 3, and 100% for groups 1 and 4, with no significant differences among groups. Mean graft **survival** time was 7.3 days for group 1, 15.5 days for group 2, 8.36 days for group 3, and 7.69 days for group 4, with significant differences between group 2 and the other groups. Systemic CsA levels were only detectable in group 2. Conclusions. CsA formulated in migliol oil delayed corneal rejection onset, but blood levels were evident in this group. CsA loaded-nanocapsules showed no effect on rejection and the drug was not detectable in blood. These data, along with the current concepts on **corneal graft rejection** immunology, suggest that the immunomodulatory effect of topical CsA in the prevention of **corneal graft rejection** may be systemically mediated.

L21 ANSWER 21 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

1997:289005 Document No.: PREV199799588208. Mycophenolate mofetil (MPM) as single therapy and in combination with ciclosporin A (CSA) in the

and Ophthalmology, Parts 1 & 2. Fort Lauderdale, ... 1997.
CODEN: IOVSDA. ISSN: 0146-0404. Language: English.

L21 ANSWER 22 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
97:26750 The Genuine Article (R) Number: VZ427. Anterior chamber-associated immune deviation promotes corneal allograft **survival**.
Niederkorn J Y (Reprint); Mellon J. UNIV TEXAS, SW MED CTR, DEPT OPHTHALMOL, 5323 HARRY HINES BLVD, DALLAS, TX 75235 (Reprint). INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (DEC 1996) Vol. 37, No. 13, pp. 2700-2707. Publisher: LIPPINCOTT-RAVEN PUBL. 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106. ISSN: 0146-0404. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Purpose, To determine whether anterior chamber-associated immune deviation (ACAID) promotes corneal allograft **survival**.

Methods, CB6F1 mice were grafted with orthotopic corneal transplants from C3H donors (mismatch at the entire major histocompatibility complex plus multiple minor histocompatibility loci) and from NZB donors (mismatch only at multiple minor histocompatibility loci). ACAID was induced by priming in the anterior chamber (AC) with either Ia(-) spleen cells, Ia(+) spleen cells, corneal endothelial cells, or corneal epithelial cells from corneal allograft donors before orthotopic **transplantation**. The role of ACAID in promoting corneal allograft **survival** was examined by determining the fate of corneal allografts in splenectomized and eusplenic mice.

Results. Anterior chamber priming produced a modest enhancement of the **survival** of fully allogeneic C3H corneal allografts. By contrast, AC priming with Ia(-) NZB spleen cells or NZB corneal endothelial cells results in the permanent acceptance of NZB **corneal grafts** in 60% and 90% of the CB6F1 hosts, respectively. Abolition of ACAID by splenectomy resulted in a sharp increase in the incidence of **graft rejection** in donor-host combinations involving multiple minor histocompatibility disparity.

Conclusions, Anterior chamber priming with alloantigens promotes corneal allograft **survival** in nonimmune and preimmune hosts. Disruption of the camero-splenic axis prevents the induction of ACAID and greatly increases the risk for corneal allograft rejection.

L21 ANSWER 23 OF 32 MEDLINE on STN
97109399. PubMed ID: 8951679. FK-506 delays **corneal graft rejection** in a model of corneal xenotransplantation. Benelli U; Lepri A; Del Tacca M; Nardi M. (Department of Neurosciences, University of Pisa, Italy.) Journal of ocular pharmacology and therapeutics : official journal of the Association for Ocular Pharmacology and Therapeutics, (1996 Winter) 12 (4) 425-31. Journal code: 9511091. ISSN: 1080-7683. Pub. country: United States. Language: English.
AB FK-506 is a relatively new immunosuppressant similar in action to cyclosporine A, but is much more potent. Its primary action is against T lymphocytes, the major cellular component in corneal allograft rejection. The purpose of this study was the evaluation of the ability of topical and systemic FK-506 in preventing corneal xenograft rejection in an experimental animal model. Cross-species xenotransplants were used as the most vigorous stimulus to induce corneal rejection. Corneas derived from Hartley guinea pigs were transplanted into the left eyes of 32 male Lewis **rats**. Topical treatment was administered by using FK-506 0.3

transplantation. [illegible] 6.75 +/- 0.31 (topical vehicle) and after 7.37 +/- 0.32 (systemic vehicle) days. The FK-506-treated groups showed allograft rejection after 14 +/- 0.88 (topical FK-506) or after 16.25 +/- 1.23 (systemic FK-506) days. In addition, FK-506-treated **rats** manifested less corneal neovascularization than control animals. We conclude that systemic or topical FK-506 is effective in prolonging xenograft **survival** in the **rat keratoplasty** model.

L21 ANSWER 24 OF 32 MEDLINE on STN

95122330. PubMed ID: 7822159. Effect of topically applied anti-CD4 monoclonal antibodies on orthotopic corneal allografts in a **rat** model. Pleyer U; Milani J K; Dukes A; Chou J; Lutz S; Ruckert D; Thiel H J; Mondino B J. (Jules Stein Eye Institute, UCLA School of Medicine.) Investigative ophthalmology & visual science, (1995 Jan) 36 (1) 52-61. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE. Monoclonal antibodies (mAb) have generated interest as therapeutic agents. Limited data are available on the treatment of **corneal graft rejection**. The purpose of this study was to assess the use of topically applied mAb on experimental **corneal grafts**. METHODS. W 3/25, an IgG 1 mouse antirat mAb that recognizes a CD4+ cell subset, was used to treat Lewis recipient **rats** that received orthotopic **corneal grafts** of Wistar-Furth donors. Recipients were randomly assigned to receive topically applied drops of liposome-incorporated anti-CD4 mAb (LIP-anti-CD4 mAb), an equivalent amount of free anti-CD4 mAb, an isotype-matched control mAb encapsulated in liposomes (LIP-control mAb), or empty liposomes (emp-LIP) 5 times daily for 10 days. To investigate the immunologic effect of mAb treatment, flow cytometry of the targeted cells and cytotoxic activity of lymphocytes were analyzed. RESULTS. Application of LIP-anti-CD4 mAb was effective in reducing the rejection rate ($P < .05$) and in prolonging the mean **survival** time of **corneal grafts** that underwent rejection ($P < .05$). In contrast, no significant effect on graft outcome was observed after the application of control agents. Flow cytometry analysis did not reveal systemic depletion of the targeted lymphocyte subset in any anti-CD4 mAb treated animals. Rejected grafts elicited a cellular cytotoxic immune response in a cell-mediated lymphocytotoxic assay independent of the treatment given. CONCLUSION. The results suggest that treatment with topically applied LIP-anti-CD4 mAb prolongs graft **survival** in orthotopic **corneal grafts** in a **rat** model. The beneficial effect of LIP-anti-CD4 mAb, probably due to enhanced intraocular delivery, was achieved by using relatively low doses of mAb.

L21 ANSWER 25 OF 32 MEDLINE on STN

94375224. PubMed ID: 8088966. Promotion of corneal allograft **survival** with leflunomide. Niederkorn J Y; Lang L S; Ross J; Mellon J; Robertson S M. (Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas 75235.) Investigative ophthalmology & visual science, (1994 Sep) 35 (10) 3783-5. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE. The efficacy of the antirejection drug leflunomide was evaluated in a **rat** model of penetrating **keratoplasty**. METHODS. **Corneal grafts** from inbred Lewis **rats** were transplanted orthotopically to inbred Wistar-Furth (WF) recipients. WF **rats** received either Leflunomide (HWA 486), the active metabolite

survival time. Moreover, almost one third of the grafts survived for an additional 3 weeks, even after drug treatment was discontinued. CONCLUSION. The results indicate that leflunomide holds considerable promise as an antirejection drug for use in recipients of corneal transplants in whom cyclosporin A and steroids are contraindicated.

L21 ANSWER 26 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
1994:315411 Document No. 120:315411 Immunosuppressive effect of topical FK506 on penetrating **keratoplasty** in **rats**. Hikita, Naofumi (Sch. Med., Kurume Univ., Kurume, 830, Japan). Kurume Igakkai Zasshi, 57(1), 176-89 (Japanese) 1994. CODEN: KIZAAL. ISSN: 0368-5810.
AB Immunosuppressive effects of topical FK506 on a **corneal graft rejection** model in allogeneic inbred **rats** were investigated. Lewis **rats** were used for recipients and Fisher **rats** for donors. All **rats** received i.p. of FK506 (0.3 mg/kg/day) for 7 days in order to ensure baseline parameters. **Rats** were then assigned randomly to the treatment group (0.3% FK506) and the control (placebo) group. The eyedrops were given every 4 h for 2 wks. **Corneal grafts** were evaluated with clin. observation, histol. and immunohistol. studies. All the **corneal grafts** in the control group were rejected by day 14 after surgery while 1/3 of **corneal grafts** in the treated group survived by day 30 and the difference in the **survival** rate between the 2 groups was statistically significant ($p < 0.009$) on day 13. The immunohistochem. observations in the FK506-treated **corneal grafts** were characterized by reduced number of CD4+ cells and a reduction in the expression of MHC class I antigens and MHC class II antigens and LFA-1. These data suggest that topical FK506 treatment is effective in preventing **corneal graft rejection** in th Lewis **corneal graft** model.

L21 ANSWER 27 OF 32 MEDLINE on STN
93315305. PubMed ID: 7686893. Effects of the immunosuppressant FK506 on a penetrating **keratoplasty** rejection model in the **rat**. Nishi M; Herbort C P; Matsubara M; Morishita Y; Nishimura M; Nieda M; Mori S; Mochizuki M. (Department of Ophthalmology, Escola Paulista de Medicina, Sao Paulo, Brazil.) Investigative ophthalmology & visual science, (1993 Jul) 34 (8) 2477-86. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.
AB PURPOSE. The immunosuppressive effects of FK506 on allogeneic corneal **transplantation** were tested in a **rat** model. METHODS. Inbred-strain Lewis **rats** were used as recipients, and Fisher **rats** were used as donors. Intraperitoneal injection of FK506 (0.3, 1.0, and 3.0 mg/kg per day) was administered for 2 weeks, and the grafts were inspected by clinical evaluation. Mixed lymphocyte culture assay, using lymphocytes from recipients of penetrating **keratoplasty** as responder cells and irradiated splenocytes from naive Fisher or Brown Norway as stimulator cells, was used to identify allogeneic stimulation. The rejection process was studied by histology and immunohistochemistry. RESULTS. The **rat** strain combination developed 100% **graft rejection** in about 2 weeks after the penetrating **keratoplasty**. FK506 prolonged the graft **survival** in a dose-dependent manner, as observed by clinical evaluation. In mixed lymphocyte culture assay, Lewis **rats** that had been primed to allogeneic stimulation at the time of cornea **transplantation** presented significant proliferation to Fisher stimulator splenocytes. FK506 suppressed this primed lymphocyte

had less intense cell infiltration than the control corneas. These data indicate that FK506 prolonged the **corneal graft survival** and can be a potentially useful drug in the immunotherapeutic arsenal to suppress **corneal graft rejection.**

L21 ANSWER 28 OF 32 MEDLINE on STN
93288366. PubMed ID: 8510902. Prolongation of corneal allograft **survival** with liposome-encapsulated cyclosporine in the **rat** eye. Milani J K; Pleyer U; Dukes A; Chou H J; Lutz S; Ruckert D; Schmidt K H; Mondino B J. (Jules Stein Eye Institute, University of California, School of Medicine, Los Angeles.) Ophthalmology, (1993 Jun) 100 (6) 890-6. Journal code: 7802443. ISSN: 0161-6420. Pub. country: United States. Language: English.

AB PURPOSE: To study the effects of different formulations of topical cyclosporine (Cyclosporin A [CsA]) on corneal allograft rejection in a **rat** model. METHODS: Female Lewis **rats** received penetrating **keratoplasties** from female Wistar-Furth donors. A total of 78 allogeneic grafts were performed. An additional 15 syngeneic grafts (Lewis) were used as technical controls. Two CsA preparations with equivalent drug concentrations (2.1 mg/ml) were applied as drops: CsA encapsulated in large unilamellar liposomes (CsA-LIP) and CsA dissolved in olive oil (CsA-DR). Allogeneic grafts were randomly assigned to receive CsA-LIP or CsA-DR beginning on the day of surgery five times daily for 10 days. Animals without any treatment or receiving empty liposomes (EM-LIP) were used as treatment controls. Grafts were graded three times weekly and a rejection index was generated based on graft clarity, neovascularization, and vessel size. RESULTS: All syngeneic grafts remained clear over the observation period of 60 days. Rejected allogeneic grafts without any treatment and those receiving EM-LIP or CsA-DR showed a mean **survival** time (+/- standard deviation) of 14 +/- 4, 14 +/- 5, and 14 +/- 4 days, respectively. There was no significant difference in mean **survival** time between the grafts without any treatment and those in CsA-DR or EM-LIP treatment groups. The mean **survival** time of rejected grafts in animals receiving CsA-LIP was prolonged to 20 +/- 4 days. There was a significant difference in the mean **survival** time between the CsA-LIP treatment group and groups receiving CsA-DR, EM-LIP, or no treatment ($P < or = 0.05$). The Kaplan-Meier **survival** curve of the CsA-LIP treatment group was significantly different from the other experimental groups. The graft **survival** rate in the CsA-LIP group was 77%, whereas the rate was 37% in the non-treated group, 45% in the CsA-DR group, and 36% in the EM-LIP group. CONCLUSION: Encapsulation of CsA in liposomes might be a promising formulation for use in the prevention of **corneal graft rejection.**

L21 ANSWER 29 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
92:630272 The Genuine Article (R) Number: JU603. ORTHOTOPIC CORNEAL **TRANSPLANTATION** IN MICE - EVIDENCE THAT THE IMMUNOGENETIC RULES OF REJECTION DO NOT APPLY. SONODA Y; STREILEIN J W (Reprint). UNIV MIAMI, SCH MED, DEPT MICROBIOL & IMMUNOL, MIAMI, FL, 33136; UNIV MIAMI, SCH MED, DEPT IMMUNOL, MIAMI, FL, 33136. TRANSPLANTATION (OCT 1992) Vol. 54, No. 4, pp. 694-704. ISSN: 0041-1337. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The fate of orthotopic corneal transplants has been studied in inbred strains of mice. Using a surgical technique that achieves >95% success of syngeneic cornea grafts, it was determined that a high proportion of

histocompatibility antigens, with or without major [illegible]
antigens. Much lower rates of rejection (<35%) were observed when the donors of the grafts differed from recipients at class I and/or class II major histocompatibility loci. **Corneal grafts** that confronted their hosts with class II MHC alloantigens alone experienced early, acute inflammation, and eventually developed stomal neovascularization, but only a small minority of these grafts were eventually destroyed. Allogeneic corneas that were transplanted orthotopically into eyes of presensitized mice were uniformly subjected to an acute rejection process that produced opacity within three weeks; however, in a minority of instances, the inflammation and opacity subside, and after eight weeks the grafts displayed a clear, nonvascularized appearance. The high rate of success of even grossly histoincompatible orthotopic corneal allografts in mice resembles the extraordinary success of unmatched allogeneic corneas transplanted into human eyes. The results are discussed in terms of the possible mechanisms that permit orthotopic corneal allografts to enjoy significantly better **survival** than orthotopic grafts of other types of solid tissues.

L21 ANSWER 30 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
91:539074 The Genuine Article (R) Number: GG495. EFFECT OF MISMATCHES FOR MAJOR HISTOCOMPATIBILITY COMPLEX AND MINOR ANTIGENS ON **CORNEAL GRAFT-REJECTION**. NICHOLLS S M (Reprint); BRADLEY B B; EASTY D L. BRISTOL EYE HOSP, SCH MED SCI, DEPT OPHTHALMOL, UNIV WALK, BRISTOL BS8 1TD, ENGLAND (Reprint); BRISTOL EYE HOSP, DEPT OPHTHALMOL, BRISTOL, ENGLAND; BRISTOL EYE HOSP, UNITED KINGDOM TRANSPLANT SERV, BRISTOL, ENGLAND. INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (1991) Vol. 32, No. 10, pp. 2729-2734. Pub. country: ENGLAND. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The importance of minor histocompatibility genes in **corneal graft rejection** was investigated using a model that simulates the major histocompatibility complex (MHC) and minor mismatches of the human allograft more accurately than previous animal models. DA(RT1a) x LEW(RT1l)F1 hybrid **rats** were backcrossed to LEW, and the backcross generation were used as **corneal graft** recipients. Female DA(RT1a) strain animals were used as donors throughout. As in humans, the MHC disparity (a to l) between each donor-recipient pair could be controlled; minor mismatches were variable and unknown. The MHC haplotype of each backcross individual (either homozygous l/l) or heterozygous a/l) was determined. Depending on this haplotype, the transplanted DA cornea was either matched or mismatched with the recipient for MHC antigens. The average proportion of minor disparate loci was 50%, although this was variable and unknown from recipient to recipient. Some animals of each MHC type were sensitized with three subcutaneous DA strain skin grafts at intervals of 2 weeks. Prior sensitization caused more rapid **corneal graft rejection** in both MHC mismatched ($P < 0.001$) and matched ($P < 0.01$) animals. All animals in the two MHC-mismatched groups (sensitized, 26; unsensitized, 17) and most in the MHC-matched groups (sensitized, 25 of 27; unsensitized, all 13) rejected their grafts. The MHC matching resulted in a greater range of **survival** times, although the difference in **survival** in unsensitized animals between matched and mismatched groups was not significant (unsensitized, $P > 0.05$; sensitized, $P < 0.001$). Thus, minor antigens played a significant role in **corneal graft rejection** in this **rat** model, and the high rejection rate of MHC-matched grafts suggested that, as with skin, several minor genes were involved. If such genes also are

J Y. (Department of Ophthalmology, University of Texas Health [illegible]
Center, Dallas 75235.) Transplantation, (1988 Feb) 45 (2) 437-43.
Journal code: 0132144. ISSN: 0041-1337. Pub. country: United States.
Language: English.

AB We have employed a **rat** model of orthotopic corneal **transplantation** to study the characteristics of rejection and development of systemic immunity in the host. Lewis (LEW) **rats** underwent a true penetrating **keratoplasty** using Wistar-Furth (WF) donor corneas. A rejection incidence of 55% with a mean **survival** time (MST) of 17.1 days was observed using these untreated allogeneic corneas. Animals undergoing rejection of these allografts developed cytotoxic T lymphocytes (CTL) capable of lysing WF lymphoblasts in a standard 51-chromium release assay. These same **rats** did not have delayed-type hypersensitivity (DTH) responses when compared to skin grafted controls. **Rats** with clear allografts had no demonstrable CTL or DTH activity. As expected, LEW **rats** that were preimmunized with WF skin grafts and subsequently received WF orthotopic **corneal grafts** rejected 100% of these corneas at an accelerated rate (MST = 9.7 days, P less than .02). We then employed a previously described technique of using latex beads to induce migration of Langerhans cells into the central cornea of the donor graft prior to **transplantation**. The presence of Langerhans cells in the donor cornea resulted in a higher incidence of rejection (96%) and an accelerated rate (MST = 11.8 days, P less than .02) when compared to untreated allografts. These **rats** also had a higher level of CTL activity and marked DTH responses. These data show that rejection of orthotopic allogeneic corneas is accompanied by the development of systemic alloimmunity as measured by CTL activity. However, these fully allogeneic corneas can be rejected in the absence of DTH responses. Langerhans cells have a dramatic effect on graft **survival** and are necessary for induction of DTH responsiveness in the host.

L21 ANSWER 32 OF 32 MEDLINE on STN

87157580. PubMed ID: 3548812. Topical steroid, cyclosporin A, and the outcome of **rat** corneal allografts. Williams K A; Erickson S A; Coster D J. British journal of ophthalmology, (1987 Mar) 71 (3) 239-42. Journal code: 0421041. ISSN: 0007-1161. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The effects of a combination of topical corticosteroid and cyclosporin A on **corneal graft survival** were tested in a model of penetrating **keratoplasty** in the inbred **rat**. Topical medications were applied four times daily to the graft for 28 days postgraft. Neither topical steroid (1% prednisolone acetate) nor topical cyclosporin (1% in chremophor EL/ethanol) was able to modify the overall incidence of rejection, though all steroid-containing medications delayed the onset of rejection significantly. The combined formulation of steroid plus cyclosporin A caused a reduction in the incidence of rejection which did not reach statistical significance and which did not eliminate the response in all animals. The chremophor/ethanol vehicle was reasonably well tolerated but did cause some periocular dermatitis.

=> s corneal graft survival
L22 360 CORNEAL GRAFT SURVIVAL

=> s l22 and treatment

L25 0 L23 AND VEGFR-3

=> dup remove l23
PROCESSING COMPLETED FOR L23
L26 51 DUP REMOVE L23 (62 DUPLICATES REMOVED)

=> d l26 1-51 cbib abs

L26 ANSWER 1 OF 51 MEDLINE on STN DUPLICATE 1
2003575042. PubMed ID: 14657695. Significant prolongation of orthotopic **corneal-graft survival** in FTY720-treated mice.
Zhang Er-Ping; Muller Anja; Ignatius Ralf; Hoffmann Friedrich. (Department of Ophthalmology, University Hospital Benjamin Franklin, Free University of Berlin, Berlin, Germany.) Transplantation, (2003 Nov 27) 76 (10) 1511-3. Journal code: 0132144. ISSN: 0041-1337. Pub. country: United States. Language: English.
AB BACKGROUND: The novel immunomodulator, FTY720, mainly acts through sequestering of lymphocytes to secondary lymphatic tissue, thereby suppressing their infiltration into grafted organs. This study aimed to investigate its influence on **corneal-graft survival**. METHODS: Sixteen BALB/c mice (H-2d) received corneal transplants from C3H (H-2k) mice. Eight mice were treated with FTY720 (10 mg/kg per day) orally from day -1 to day 11, and all animals received 0.1% dexamethasone eye drops for the same time. In addition, eyes and regional lymph nodes from similarly treated animals were subjected to immunohistochemistry and proliferation assays. RESULTS: FTY720 significantly prolonged graft survival from 28+/-8.1 to 36.5+/-7.1 days (P=0.021). In treated animals, corneal infiltration by CD4+ and F4/80+ cells was reduced from 70.8+/-60.3 to 7.0+/-9.0 (P=0.004) and from 97.5+/-30.7 to 44.8+/-24.9 (P=0.01) cells, respectively, and allogeneic T-cell proliferation was decreased. CONCLUSIONS: FTY720 **treatment** substantially protects corneal allografts and may provide an immunomodulatory strategy in clinical corneal transplantation.

L26 ANSWER 2 OF 51 MEDLINE on STN DUPLICATE 2
2003335729. PubMed ID: 12867398. Long-term graft survival after penetrating keratoplasty. Thompson Robert W Jr; Price Marianne O; Bowers Patrick J; Price Francis W Jr. (Price Vision Group, Indianapolis, Indiana, USA.) Ophthalmology, (2003 Jul) 110 (7) 1396-402. Journal code: 7802443. ISSN: 0161-6420. Pub. country: United States. Language: English.
AB PURPOSE: To determine long-term graft survival rates and causes of secondary graft failures for a large series of penetrating keratoplasties (PKPs). DESIGN: Retrospective, noncomparative case series. PARTICIPANTS: Longitudinal review of 3992 consecutive eyes that underwent PKP at a large tertiary care referral center from 1982 through 1996. Data were collected retrospectively from August 1982 through December 1988 and prospectively thereafter. INTERVENTION: Three thousand six hundred forty primary grafts and 352 regrafts. MAIN OUTCOME MEASURES: **Corneal graft survival** and etiology of graft failures. Patients were evaluated preoperatively and at 1, 3, 6, 9, 12, 18, and 24 months after transplant, then at yearly intervals. RESULTS: Mean recipient age was 67 years (range, 1-98 years). The predominant indications for PKP were pseudophakic bullous keratopathy (32%) and Fuchs' dystrophy (23%). Graft failure occurred in 10% (385) of the eyes. The most common causes of secondary graft failure were endothelial failure (29%) or immunologic endothelial rejection (27%). Survival of first time grafts was 90% at 5 years and 82% at 10 years. Initial regrafts had significantly lower

survival rates in this series demonstrate that [illegible]
treatment for the corneal diseases commonly transplanted in the United States. However, endothelial failure and immunologic graft rejection were persistent risks over the long term, supporting the need for continued patient follow-up. Regrafts, aphakic eyes without intraocular lens placement at the time of transplant, and corneas with deep stromal vascularization had reduced graft survival rates. Pseudophakic bullous keratopathy grafts with a retained posterior chamber intraocular lens were at increased risk of endothelial failure compared with primary grafts done for other causes or compared with pseudophakic bullous keratopathy grafts done with intraocular lens exchange.

L26 ANSWER 3 OF 51 MEDLINE on STN
2003446938. PubMed ID: 14507748. Penetrating keratoplasty in children: visual and graft outcome. McClellan K; Lai T; Grigg J; Billson F. (Department of Clinical Ophthalmology and Save Sight Institute, University of Sydney, GPO Box 4337, Sydney NSW 2001, Australia.. kathy@eye.usyd.edu.au) . British journal of ophthalmology, (2003 Oct) 87 (10) 1212-4. Journal code: 0421041. ISSN: 0007-1161. Pub. country: England: United Kingdom. Language: English.

AB AIMS: To review factors affecting graft survival and determinants of visual acuity after penetrating keratoplasty in children. METHODS: All cases of penetrating keratoplasty performed in an ophthalmic unit, in children aged less than 15 years at the time of operation, for the period 1984 to 2002 were included. RESULTS: 19 penetrating keratoplasties were done in 18 eyes of 16 children, age range 2 weeks to 14 years 8 months (mean 9.24 years), with mean follow up 6.6 years. 73.7% of grafts have remained clear for up to 14 years. Postoperative visual acuity among congenital indications for graft was better than 6/60 in only 14.2% of cases, but was better than or equal to 6/12 in all cases of keratoconus. CONCLUSION: This series shows that prolonged **corneal graft survival** can be achieved in children, but successful restoration of visual acuity depends upon a period of normal visual development before the onset of corneal opacification.

L26 ANSWER 4 OF 51 MEDLINE on STN DUPLICATE 3
2003567597. PubMed ID: 14566570. Ballistic CTLA4 and IL-4 gene transfer into the lower lid prolongs orthotopic **corneal graft survival** in mice. Zhang Er-Ping; Franke Jurgen; Schroff Matthias; Junghans Claas; Wittig Burghardt; Hoffmann Friedrich. (Department of Ophthalmology, University Hospital Benjamin Franklin, Free University of Berlin, Hindenburgdamm 30, 12203, Berlin, Germany.) Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie, (2003 Nov) 241 (11) 921-6. Journal code: 8205248. ISSN: 0721-832X. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB PURPOSE: To explore outflow from the eye and to determine and modulate the influence of lymphatic drainage on **corneal graft survival** in mice. METHODS: Tracer experiments were conducted in BALB/c mice using the (99m)Tc colloidal albumin Nanocoll. Count rates were determined in the eyes, submandibular lymph nodes, spleen, liver and blood 24 h after subconjunctival, intracorneal, intracameral (anterior chamber), intravenous and subcutaneous lower-lid or upper-lid injections (n=6 each). Four groups of BALB/c mice (n=8) received corneal transplants from C3H mice; two of them were treated ballistically with vector CTLA4+IL-4 onto the leg or the lower lid, one group was untreated and the other control group was treated with an empty minimalistic,

(71.2%) injection. Vector [illegible] **treatment** [illegible]
but not of the leg prolonged graft survival (P=0.004). CONCLUSION: These tracer studies confirmed for the first time identical lymphatic drainage from the cornea and the lower lid. Logically, lymphatic drainage could be manipulated and graft survival improved by gene transfer to the lower lid.

L26 ANSWER 5 OF 51 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2004:67700 Document No.: PREV200400066922. FK 506 and aminoguanidine suppress iNOS induction in orthotopic corneal allografts and prolong graft survival in mice. Strestikova, P. [Reprint Author]; Plskova, J.; Filipec, M.; Farghali, H.. 1st Faculty of Medicine, Institute of Pharmacology, Charles University, Prague, Czech Republic. pstres@lf1.cuni.cz. Nitric Oxide, (September 2003) Vol. 9, No. 2, pp. 111-117. print.
ISSN: 1089-8603. Language: English.
AB The aim of this study was to compare the effectiveness of immunosuppressant FK 506 and the specific inhibitor of inducible nitric oxide synthase (iNOS) aminoguanidine (AG) in prevention of corneal graft rejection and to investigate the iNOS expression in the rejection process. Orthotopic corneal allografting in mice was performed (C57BL/10; H-2b to BALB/c; H-2d). FK 506 (0.3 mg/kg per day) or AG (100 mg/kg per day) was injected intraperitoneally for 4 weeks. Grafted mice without therapy served as controls. Immunohistological evaluation of iNOS-positive cells and macrophage infiltration in grafts 27th day after grafting was performed. Within 4 weeks FK 506 prevented graft rejection in 71% and AG in 57% of animals compared to 29% of clear grafts in controls. A significant proportion of iNOS-positive cells was detected in the rejected grafts of the control and AG-treated groups. The **treatment** with FK 506 resulted in the inhibition of iNOS expression to a high degree in the rejected corneas. Non-rejected corneas of all groups and non-transplanted corneas exhibited no iNOS-positive cells. A massive infiltration of macrophages was detected in the rejected grafts, whereas non-rejected grafts exhibited only slight infiltration of macrophages. The presented data suggest that overexpression of iNOS and/or activation of iNOS is one of the several influential factors that contribute to the rejection process and that iNOS suppression delays corneal allograft rejection. FK 506 and AG are effective drugs in preventing corneal allograft rejection. Higher beneficial effect of FK 506 on graft survival could be explained by its well-known selective T-cell immunosuppression.

L26 ANSWER 6 OF 51 MEDLINE on STN DUPLICATE 4
2003118267. PubMed ID: 12631232. The potential of antibody-based immunosuppressive agents for corneal transplantation. Thiel Michael A; Coster Douglas J; Williams Keryn A. (Department of Ophthalmology, Flinders University of South Australia, Adelaide, Australia.) Immunology and cell biology, (2003 Apr) 81 (2) 93-105. Ref: 205. Journal code: 8706300. ISSN: 0818-9641. Pub. country: Australia. Language: English.
AB Corneal transplantation is a sight-restorative procedure but its success is limited by irreversible graft rejection, which accounts for up to 50 per cent of failures. The normal eye is an immune-privileged site. Multiple mechanisms maintain ocular privilege, including the blood-eye barrier, the lack of blood vessels and lymphatics in the normal cornea, the relative paucity of mature antigen-presenting cells in the central cornea, the presence of immunomodulatory factors in ocular fluids, and the constitutive expressive of CD95L (Fas ligand) within the eye. However, privilege can be eroded by the sequelae of inflammation and neovascularization. Corneal graft rejection in humans is currently suppressed with topical glucocorticosteroids, which are moderately

antibodies have shown promise as [illegible]
corneal graft survival in experimental animal models, and may eventually prove to be useful adjuncts to corticosteroids.

L26 ANSWER 7 OF 51 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2003:554765 Document No.: PREV200300552023. THE EFFECT OF LOCAL AND SYSTEMIC ADMINISTRATION OF SOLUBLE IL - 15 RECEPTOR alpha - CHAIN IN EXPERIMENTAL CORNEAL TRANSPLANTATION . Kuffova, L. [Reprint Author]; Taylor, J. A. [Reprint Author]; Duncan, L. [Reprint Author]; Liew, F. Y.; Wei, X. Q.; Forrester, J. V. [Reprint Author]. Dept Ophthalmol, Univ Aberdeen, Aberdeen, UK. ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 4663. cd-rom.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
Language: English.
AB Purpose: To investigate and compare the effects of local and systemic administration of sIL-15 receptor alpha-chain (sIL-15Ralpha) in a mouse model of corneal transplantation. Method: In a model of murine allografting (C57BL10 mice (H2b) to BALB/c mice (H2d)) we treated recipients of the grafts as follows: (1) topical **treatment** with sIL-15Ralpha (3x per day for 20 days); (2) systemic **treatment** i.p. using 3 different schedules: (a) sIL-15Ralpha or control non-sense M4 protein or PBS from day 0-20 post-graft at a dose of 60gammag/day/animal; (b) sIL-15Ralpha or M4 protein from day 0 -10 post-graft; and (c) sIL-15Ralpha or M4 protein from day 5-15 after corneal grafting. Immunohistochemistry of donor corneas after local **treatment** and CBA from the DLN was performed at 3, 6 and 9d post-graft. Results: Systemic **treatment** with sIL-15Ralpha using both the 0-20 and 0-10 days post-graft protocol significantly prolonged **corneal graft survival**. Control administration of non-sense M4 protein had no effect on prolongation of **corneal graft survival** compared to untreated (PBS) controls. In contrast, administration of sIL-15Ralpha using the 5-15 days post graft protocol led to an accelerated tempo of corneal graft rejection. Local **treatment** with sIL-15Ralpha significantly prolonged graft survival in comparison with non-treated or M4 protein treated graft recipients. Immunohistochemistry showed reduced F4/80+, CD11b+, MoMa-2+ and mannose receptor positive macrophage infiltration of corneal grafts topically treated with sIL-15Ralpha. No statistically significant difference was found in production of IFN-gamma, TNF-alpha and IL-6 by cells from DLN between groups treated with sIL-15Ralpha and M4 protein. However, the production of IL-12p70, IL-10 and MCP-1 was significantly higher in the group treated with sIL-15Ralpha than treated with M4 protein. Conclusions: These results indicate that IL-15-IL-15R blockade is effective in delaying corneal graft rejection when used both systematically and topically. In both cases, the effect was observed only when blockage was in place from the time of grafting.

L26 ANSWER 8 OF 51 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2003:554760 Document No.: PREV200300552018. DENDRITIC CELL - BASED TOLERANCE INDUCTION IN A MURINE MODEL OF CORNEAL ALLOGRAFT REJECTION. Cai, L. [Reprint Author]; Lumsden, L. [Reprint Author]; Duncan, L. [Reprint Author]; Muckersie, E. [Reprint Author]; Forrester, J. V. [Reprint Author]. Ophthalmology, University of Aberdeen, Aberdeen, UK. ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 4658. cd-rom.

Our aim was to evaluate the role of syngeneic immature DC in induction in a murine model of corneal allograft rejection. Methods: DCs were enriched from bone marrow cultures in the presence granulocyte-macrophage colony-stimulating factor (GM-CSF) and transforming growth factor beta 2 (TGFbeta-2). PBS or 106TGFbeta-treated DC were injected subcutaneously into the nape of the neck (s.c.) of syngeneic recipient mice and corneal allografts were performed seven days after s.c. injection. Three days post corneal transplantation, cervical lymph nodes were separately dissected as submandibular (SM) and superficial cervical (SC) lymph node (LN). Draining LN cells were tested for proliferation in an MLR and cytokine production by ELISA. The phenotype of drainging LN cells was examined by flow cytometry (FCM). The eyes were evaluated by clinical observation at various times. Results: Administration of TGFbeta-treated DC by s.c. injection induced strong proliferation and cytokine production only in SC LN cells. Low levels of IFN-gamma and high levels of IL-10 were present in MLR supernatant from cultured SC LN after DC s.c. injection. FCM analysis indicated there was a downregulation of CD3+CD4+CD44+ T cells and an upregulation of CD4+CD25+CTLA-4+ T regulatory cells (Treg) in the SC LN following TGFbeta-treated DC s.c. administration. Compared to controls, TGFbeta-DC **treatment** prolonged the mean **corneal graft survival** time significantly (16.75+-3.4d vs 26+-4.05d, P<0.01). Conclusions: This study has shown immature syngeneic DCs have the potential to prolong corneal allograft survival as DC are directed towards the SC LN, a site previously known to be involved in mucosal tolerance. Upregulation of Treg and the high amounts of Th2 cytokines in SC LN may have contributed to this protective effect.

L26 ANSWER 9 OF 51 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2003:554280 Document No.: PREV200300551555. SIGNIFICANT PROLONGATION OF ORTHOTOPIC **CORNEAL GRAFT SURVIVAL** IN FTY720 - TREATED MICE. Hoffmann, F. [Reprint Author]; Zhang, E. -P. [Reprint Author]; Mueller, A. [Reprint Author]; Ignatius, R.. Ophthalmology, Free Univ Berlin-UKBF, Berlin, Germany. ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 3450. cd-rom. Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
Language: English.

AB Purpose: The novel immunomodulator, FTY720, mainly acts through sequestering of lymphocytes to secondary lymphatic tissue, thereby suppressing their infiltration into grafted organs. This study aimed to investigate its influence on **corneal graft survival**. Methods: Sixteen BALB/c mice (H-2d) received corneal transplants from C3H (H-2k) mice. Eight mice were treated with FTY720 (10 mg/kg/d) orally from day -1 to day 11, all animals received 0.1% dexamethasone eye drops for the same time. Additionally, eyes and regional lymph nodes from similarly treated animals were subjected to immunohistochemistry and proliferation assays 29-31 days after transplantation. Results: FTY720 significantly prolonged graft survival from 28+-8.1 to 36.5+-7.1 days (p=0.021). In treated animals corneal infiltration by CD4+ and F4/80+ cells was reduced from 70.8+-60.3 to 7.0+-9.0 (p=0.004) and from 97.5+-30.7 to 44.8+-24.9 (p=0.01) cells, respectively, and allogeneic T cell proliferation of regional lymph node cells towards gamma irradiated donor spleen cells was decreased to some 43%. Conclusions: FTY720 **treatment** substantially protects corneal allografts and may provide an immunomodulatory strategy in

Claas; Wittig, Burghardt, Hoffmann, Friedrich (Klinik ...
Universitatsklinikum Benjamin Franklin, Freie Universitat Berlin, Hindenburgdamm 30, Berlin, 12200, Germany). Graefe's Archive for Clinical and Experimental Ophthalmology, 240(2), 114-119 (English) 2002. CODEN: GACODL. ISSN: 0721-832X. Publisher: Springer-Verlag.

AB The beneficial effect of modulating an allospecific immune response by ballistic IL-4 and CTLA4 gene transfer to deliver minimalistic immunol. defined gene expression (MIDGE) vectors into the corneal epithelium was demonstrated in corneal transplantation. However, side effects reduced graft survival in control animals after ballistic transfer without DNA. An adapter was constructed for the gene gun apparatus to enlarge and keep constant the distance between the gun and the cornea. Mice were treated by ballistic transfer of luciferase- or IL-10 -encoding MIDGE vectors using gold particles different in quantity, size and size uniformity. Levels of protein expression were determined Treated corneas were observed under the scanning electron microscope and immunohistol. Three groups of Balb/c (H-2d) mice received a C3H (H-2 k) corneal graft and two of them had gold particles delivered into the corneal epithelium by gene gun. Using the gene gun and the distance piece, SEM did not reveal morphol. differences of the corneal surface compared with untreated corneas on day 2 and 5. Sagittal histol. sections of the central cornea did not show an invasion of macrophages 24 h after **treatment**. The expression of luciferase and IL-10 was not reduced when a smaller amount of gold (0.1 mg instead of 0.5 mg) was employed. Ballistic gold **treatment** did not reduce graft survival. Ballistic gene transfer into the corneal epithelium allows high cytokine expression in the cornea without measurable side effects if an apparatus is used that is adapted for this specific purpose.

L26 ANSWER 11 OF 51 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

2003:164951 Document No.: PREV200300164951. Promoting Corneal Allograft Survival Through Oxidative Macrophage Induction. Yamada, J. [Reprint Author]; Maruyama, K.; Sano, Y.; Kinoshita, S.; Murata, Y.; Hamuro, J.. Ophthalmology, Kyoto 2nd Red Cross Hospital, Kyoto, Japan. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 2270. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: On the basis of functional distinction and intracellular content of glutathione, macrophages are categorized into reductive macrophages (RMp) and oxidative macrophages (OMp). The balance between the two types is known to regulate Th1/Th2 balance through the cytokine production differential. Since Th2 bias promotes corneal allograft survival, we examined the fate of corneal allografts in mice subject to the influence of OMp, which can lead Th2 type differentiation. Methods: Either 200 mug of OMp inducer (N,N'-diacetyl-L-cystine dimethylester ((NACOMe)2)) or saline alone (control) was injected intraperitoneally into BALB/c (H-2d) recipients on days 0, 4 and 7 prior to penetrating keratoplasty. C57BL/10 (H-2b, MHC and minor H disparate) or B10.D2 (H-2d, MHC-matched) corneal grafts were placed on neovascularized recipient graft beds and assessed clinically. B10.D2 grafted recipients were evaluated for donor-specific delayed-type hypersensitivity (DTH) and their splenocytes were examined for donor-specific cytokine production (IFN-gamma, IL-4, IL-10) in vitro at 1 and 2 weeks postoperatively. In other experiments, 20 million splenocytes from (NACOMe)2-treated recipients that had clear B10.D2 allografts for 2 weeks were adoptively transferred to naive BALB/c mice;

donor-specific DTH, their splenocytes showing the type [illegible]. However, (NACOMe)2-treated mice did not acquire DH ($p < 0.01$); their splenocytes showed various types of response, such as Th1 (n = 2), Th0 (n = 3), and Th2-like (n = 1). Moreover, adoptive transfer of splenocytes from (NACOMe)2-treated mice did not promote corneal allograft survival. Conclusion: OMp induction promotes minor H only incompatible, but not total disparate, **corneal graft survival,** which promotion may depend on suppression of innate immunity and abolition of indirect pathway allorecognition.

L26 ANSWER 12 OF 51 MEDLINE on STN DUPLICATE 5

2001354619. PubMed ID: 11254685. Gamma delta T cells are needed for ocular immune privilege and **corneal graft survival.**

Skelsey M E; Mellon J; Niederkorn J Y. (Graduate Program in Immunology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA.) Journal of immunology (Baltimore, Md. : 1950), (2001 Apr 1) 166 (7) 4327-33. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB It has been recognized for over a century that the anterior chamber of the eye is endowed with a remarkable immune privilege. One contributing component is the Ag-specific down-regulation of systemic delayed-type hypersensitivity (DTH) that is induced when Ags are introduced into the anterior chamber. This phenomenon, termed anterior chamber-associated immune deviation (ACAID), culminates in the generation of regulatory cells that inhibit the induction (afferent suppression) and expression (efferent suppression) of DTH. Since gamma delta T cells play a major role in other forms of immune regulation, we suspected they might contribute to the induction and expression of ACAID. Mice treated with anti-gamma delta Ab failed to develop ACAID following anterior chamber injection of either soluble Ag (OVA) or alloantigens (spleen cells). Additional experiments with knockout mice confirmed that mice lacking functional gamma delta T cells also fail to develop ACAID. Using a local adoptive transfer of DTH assay, we found that gamma delta T cells were required for the generation of regulatory T cells, but did not function as the efferent regulatory cells of ACAID. The importance of gamma delta T cells in corneal allograft survival was confirmed by blocking gamma delta T cells with GL3 Ab before corneal transplantation. While in vivo **treatment** with normal hamster serum had no effect on **corneal graft survival,** infusion of anti-gamma delta Ab resulted in a profound increase in corneal allograft rejection. Thus, gamma delta T cells are needed for sustaining at least one aspect of ocular immune privilege and for promoting corneal allograft survival.

L26 ANSWER 13 OF 51 MEDLINE on STN DUPLICATE 6

2001667212. PubMed ID: 11713065. **Corneal graft survival** and intraocular pressure control after penetrating keratoplasty and glaucoma drainage device implantation. Arroyave C P; Scott I U; Fantes F E; Feuer W J; Murray T G. (Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida 33101, USA.) Ophthalmology, (2001 Nov) 108 (11) 1978-85. Journal code: 7802443. ISSN: 0161-6420. Pub. country: United States. Language: English.

AB OBJECTIVE: To investigate **corneal graft survival** rates and intraocular pressure (IOP) control in eyes after penetrating keratoplasty (PK) and glaucoma drainage device (GDD) implantation. DESIGN: Retrospective, comparative, consecutive case series. PARTICIPANTS: All patients who underwent PK and GDD implantation

placed in the anterior chamber in 34 eyes (75%), and [illegible] in 18 eyes (25%). Preoperative IOP was 11 to 53 mmHg with or without antiglaucoma medications in 16 eyes (30%) with the GDD implanted in the anterior chamber and in 4 eyes (22%) with the GDD placed in the vitreous cavity (P = 0.76). At 1 year after GDD implantation, the graft was clear in 26 eyes (48%) with the GDD in the anterior chamber compared with 15 eyes (83%) with the GDD in the vitreous cavity (P = 0.013). Forty-eight eyes (89%) with the GDD in the anterior chamber and 18 eyes (100%) with the GDD in the vitreous cavity had IOP between 5 and 21 mmHg with or without antiglaucoma medications (P = 0.33). The mean reduction in IOP, 1 year after surgery, was 12 mmHg among eyes with the GDD in the anterior chamber, compared with 17 mmHg among eyes with the GDD in the vitreous cavity (P = 0.13) CONCLUSIONS: **Corneal graft survival** at 1 year is significantly higher among eyes with the GDD implanted in the vitreous cavity compared with those in which the GDD is implanted in the anterior chamber. The IOP was significantly lower at 1 year after surgery compared with before surgery in both groups, and there was no significant difference between the groups in IOP control and amount of IOP reduction. There was no significant difference in **corneal graft survival** or IOP control between eyes with the GDD implanted concurrently with the PK versus after the PK.

L26 ANSWER 14 OF 51 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2001198065 EMBASE Pars plana tube insertion of glaucoma drainage implants and penetrating keratoplasty in patients with coexisting glaucoma and corneal disease. Sidoti P.A.; Mosny A.Y.; Ritterband D.C.; Seedor J.A.. Dr. P.A. Sidoti, Department of Ophthalmology, New York Eye and Ear Infirmary, 310 East 14th Street, New York, NY 10003, United States. psidoti@nyee.edu.
Ophthalmology 108/6 (1050-1058) 2001.
Refs: 60.
ISSN: 0161-6420. CODEN: OPHTDG.
Publisher Ident.: S 0161-6420(01)00583-8. Pub. Country: United States.
Language: English. Summary Language: English.

AB Purpose: To determine the efficacy and associated complications of glaucoma drainage implant (GDI) surgery with pars plana tube insertion and penetrating keratoplasty (PK) in eyes with glaucoma and corneal disease. Design: Retrospective, interventional case series. Participants: All patients who underwent both GDI surgery with pars plana tube insertion and PK before September 1997 were included. Methods: The medical records of 34 consecutive patients (34 eyes) who had undergone GDI (Baerveldt, Pharmacia & Upjohn, Kalamazoo, MI; Molteno, IOP Inc., Costa Mesa, CA; Krupin, Hood Laboratories, Pembroke, MA; or Ahmed, New World Medical, Rancho Cucamonga, CA) insertion before, concurrent with, or after PK were reviewed retrospectively. All corneal grafts were clear before GDI surgery for patients who underwent glaucoma surgery after PK. Outcomes were evaluated using Kaplan-Meier life-table analysis. Main Outcome Measures: Clinical outcome assessment included corneal graft clarity, intraocular pressure (IOP), visual acuity, and identification of complications. Results: Mean follow-up after completion of both GDI surgery and PK was 12.1 ± 8.4 months (range, 0-31.8 months). Twelve- and 24-month life-table rates for complete success after both GDI and PK were 63% and 33%, respectively. Twelve- and 24-month life-table success rates for IOP control and corneal graft clarity were 85% and 62%, and 64% and 41%, respectively. Final postoperative visual acuity was the same as or better than (≥2 Snellen lines) the preoperative level in 29 patients (85%). One or more posterior segment complications occurred in 15 (44%) patients.

plana versus anterior segment tube placement [illegible]
investigation. .COPYRGT. 2001 by the American Academy of Ophthalmology.

L26 ANSWER 15 OF 51 MEDLINE on STN DUPLICATE 7
2002063739. PubMed ID: 11789866. Contribution of lymphatic drainage system in corneal allograft rejection in mice. Hoffmann F; Zhang E P; Mueller A; Schulte F; Foss H D; Franke J; Coupland S E. (Department of Ophthalmology, University Hospital Benjamin Franklin, Free University Berlin, Germany.. fhoffman@zedat.fu-berlin.de) . Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie, (2001 Nov) 239 (11) 850-8. Journal code: 8205248. ISSN: 0721-832X. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB PURPOSE: To modulate aqueous outflow via the uveoscleral pathway and to determine its influence on **corneal graft survival** in mice. METHODS: BALB/c mice received corneal transplants from C3H mice and were placed randomly in three **treatment** groups: saline, pilocarpine or latanoprost. Three further groups received adjuvant systemic and topical corticosteroids. The kinetics of infiltrating lymphocytes, neutrophils and macrophages in the transplants was investigated in an additional 96 animals. Cytokine expression in the submandibular lymph nodes and spleen was investigated using in-situ hybridization and RNAse protection assay. Tracer experiments were conducted using 99mTC colloidal albumin Nanocoll; count rates were determined in the submandibular lymph nodes, spleen and blood following both subconjunctival and intracameral injection. RESULTS: Neither pilocarpine nor latanoprost had any influence on aqueous outflow or allograft survival in mice. Neutrophils and macrophages dominated the infiltrating cells 11 days postoperative in both treated and untreated grafts. On postoperative day 13, a greater increase in lymphocytes than in other cell groups was observed in allogeneic grafts. Following allogeneic transplantation, 1% of lymphocytes in ipsilateral submandibular lymph nodes were positive for IFN-gamma. Tracer studies revealed a 16% aqueous outflow via the uveoscleral routes following intracameral injection of Nanocoll; this was increased by 97% with subconjunctival injection. Conclusion: Our data confirm the existence of functional lymphatic drainage via the uveoscleral pathway and conjunctiva in the mouse. Cells within the ipsilateral submandibular lymph node respond to stimuli upstream. This reaction could potentially be manipulated to improve graft survival.

L26 ANSWER 16 OF 51 CAPLUS COPYRIGHT 2004 ACS on STN
2001:209316 Document No. 135:342936 Low-dose, short-term **treatment** with anti-CD4 monoclonal antibody prolongs corneal allograft survival. Thiel, M. A.; Takano, T.; Hawksworth, N.; Coster, D. J.; Williams, K. A. (Department of Ophthalmology, Flinders University of South Australia, Adelaide, Australia). Transplantation Proceedings, 33(1-2), 635-636 (English) 2001. CODEN: TRPPA8. ISSN: 0041-1345. Publisher: Elsevier Science Inc..

AB A study was conducted to determine whether short-term, low-dose **treatment** with anti-CD4 mAb or anti-interleukin-2 receptor (IL-2R, CD25) mAb given only during the perioperative period could prolong **corneal graft survival**. Fischer 344 rats RT1v1 received orthotropic corneal grafts from Wistar-Furth (WF) RT donor rats. Antibodies were given as i.p. injections on day -5, 0,+3, +7 with respect to transplantation. Each dose contained a control mAb to an irrelevant specificity, or 250 μg of W3/25 anti-CD4 mAb (IgG1) or a

mAb did not prolong **corneal graft survival**.

L26 ANSWER 17 OF 51 MEDLINE on STN
2002128581. PubMed ID: 11864435. An experimental study on subconjunctival interleukin-1 receptor antagonist for promotion of corneal transplant survival. Zhai C; Zhang W; Zou L; Pan Z; Li N; Wu Y; Lu L; Zhang S; Ma D. (Beijing Institute of Ophthalmology, Beijing 100005, China.) [Zhonghua yan ke za zhi] Chinese journal of ophthalmology, (2001 Jul) 37 (4) 270-2. Journal code: 16210540R. ISSN: 0412-4081. Pub. country: China. Language: Chinese.

AB OBJECTIVE: To determine whether the subconjunctival application of interleukin-1 receptor antagonist (IL-1ra) can prolong the **corneal graft survival** in the rat model of orthotopic penetrating keratoplasty. METHODS: For all experiments, F344 corneas were transplanted into LOU (major histocompatibility-disparate) eyes. Experimental groups received subconjunctival injection of 50, 100 and 200 microg IL-1ra respectively, and the control group received the same volume of 0.9% normal saline instead for consecutive 2 weeks. All transplants were evaluated for 4 weeks after surgery for signs of rejection. RESULTS: The mean survival time (MST) of the grafts of the experimental groups was increased significantly ($t = 0.00$, $P < 0.01$) in comparison with the control group. The MST of the IL-1ra 200 microg group was increased significantly than that of the IL-1ra 50 microg group ($t = 0.00$, $P < 0.01$). Furthermore, the IL-1ra-treated grafts had significantly less corneal inflammation, infiltration, lower levels of opacity, edema, neovascularization and rejection index compared with the control group. CONCLUSIONS: Subconjunctival **treatment** of IL-1ra has a significantly positive effect on promoting corneal allograft survival. And its effect is dosage-dependent.

L26 ANSWER 18 OF 51 EMBASE on STN
2001392519 EMBASE Long-term follow-up of **corneal graft survival** following bone marrow transplantation in the Maroteaux-Lamy syndrome. Ucakhan O.O.; Brodie S.E.; Desnick R.; Willner J.; Asbell P.A.. Dr. P.A. Asbell, Department of Ophthalmology, Box 1183, 5th Ave. and 100th Street, New York, NY 10029-6574, United States. CLAO Journal 27/4 (234-237) 2001.
Refs: 20.
ISSN: 0733-8902. CODEN: CLAJEU. Pub. Country: United States. Language: English. Summary Language: English.

AB Purpose: To present a case of Maroteaux-Lamy syndrome (MLS, mucopolysaccharidosis [MPS] type VI) who underwent bone marrow transplantation (BMT) for gene transfer at the age of 13, and penetrating keratoplasty at the age of 17, and maintained clear corneal grafts bilaterally for 13 years. To our knowledge, this is the longest follow-up reported on **corneal graft survival** in a patient with MLS and BMT. Methods: In 1982, BMT was successfully performed on a 13-year-old girl with MLS with growth retardation, typical facial features, skeletal and joint deformities, hepatosplenomegaly, cardiopulmonary dysfunction, and corneal clouding. Corneal transplantation was done on the left eye in 1986, and on the right eye in 1987 (6 months later) without difficulty or complication. Results: Thirteen years postoperatively, the patient was systemically well, and both eyes retained clear corneal grafts. Conclusion: BMT retarded further dysfunction from MLS, and the corneal transplants retained clarity. Further controlled studies with longer follow-up are required to establish the efficacy of

8216186. ISSN: 0277-3740. Pub. Country: United States. Language:

AB PURPOSE: To determine overall 2- and 5-year **corneal graft survival** rates and to identify risk factors for corneal graft failure in our patient population. METHODS: A retrospective chart review of 696 patients undergoing corneal transplantation performed by a single surgeon at The Toronto Western Hospital over a 7.5-year period. RESULTS: A total of 468 eyes met the inclusion criteria for this study. Overall, the 2- and 5-year graft survival rates were 78.8% and 64.5%, respectively. In a univariate analysis, patient age, gender, history of glaucoma, preoperative diagnosis, type of operative procedure, and postoperative factors all were shown to be significantly associated with graft survival. In a multivariate analysis, six independent predictors of graft failure were identified: preoperative diagnosis, neovascularization of the graft, the presence of peripheral anterior synechiae, gender, occurrence of one or more rejection episodes, and age of the recipient at the time of corneal transplantation. CONCLUSIONS: Risk of graft failure can vary substantially within a population of patients receiving a corneal transplant. The outcomes of this study concur with the risk factors for corneal graft failure in the literature and can be used as prognostic guidelines for both surgeons and patients.

L26 ANSWER 20 OF 51 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2000306055 EMBASE Ballistic transfer of minimalistic immunologically defined expression constructs for IL4 and CTLA4 into the corneal epithelium in mice after orthotopic corneal allograft transplantation. Konig Merediz S.A.; Zhang E.-P.; Wittig B.; Hoffman F.. F. Hoffmann, Freie Universitat Berlin, Universitatsklin. Benjamin Franklin, Augenklinik und Poliklinik, Hindenburgdamm 30, 12200 Berlin, Germany. fhoffman@zedat.fu-berlin.de. Graefe's Archive for Clinical and Experimental Ophthalmology 238/8 (701-707) 2000.
Refs: 27.
ISSN: 0721-832X. CODEN: GACODL. Pub. Country: Germany. Language: English. Summary Language: English.

AB Background: Experiments were performed to determine whether corneal epithelium transfected with minimalistic immunologically defined expression constructs for the extracellular fragment of CTLA4 and for interleukin-4 (IL-4) or interleukin-10 (IL-10) is able to modulate an allospecific immune response after orthotopic corneal grafting in mice. Methods: Six groups of BALB/c (H-2d) mice received a C3H (H-2k) corneal graft and dexamethasone eye drops until day 11. Five groups of BALB/c mice had gold particles delivered into the corneal epithelium by Gene Gun on day 10 after transplantation. In four groups, minimalistic immunologically defined gene expression (MIDGE) vectors were delivered into to the corneal epithelium by ballistic transfer. The levels of expressed IL-4 and IL-10 were determined by an enzyme-linked immunosorbent assay (ELISA) in shock-frozen homogenized corneas. The expression kinetics of Gene-Gun-transfected corneas were determined by measuring luciferase in lysed whole corneas at different time intervals. Results: Luciferase expression was detectable during the first 5 days following transfection. ELISA was used to determine IL-4 and IL-10 expression in corneal tissue 36 h after transfection. Ballistic IL-4 and CTLA4 gene transfer significantly prolonged **corneal graft survival** in comparison with the gold-treated control group and the IL-10-treated group. Conclusion: The beneficial effect of IL-4 and CTLA4, but not IL-10 gene transfer into the corneal epithelium by MIDGE vectors was demonstrated for the first time in corneal transplantation.

Canada.) Journal of glaucoma, (2000 Jun) 9 (3) 200-12. Journal
9300903. ISSN: 1057-0829. Pub. country: United States. Language: English.
AB PURPOSE: To determine the effects of noncontact transscleral Nd:YAG cyclophotocoagulation (NCTY) in the **treatment** of refractory glaucoma postpenetrating keratoplasty (PKP) with respect to intraocular pressure (IOP), **corneal graft survival**, and reduction of glaucoma medications. METHODS: The records of all patients treated with NCTY for refractory glaucoma after PKP at the authors' institution over an 11-year interval were reviewed. The LASAG noncontact Nd:YAG laser (Lasag AG; Thun, Switzerland) was used. Approximately 40 laser applications were delivered per eye. Visual acuity, IOP, glaucoma medications, and corneal graft clarity were evaluated. RESULTS: Fifty-two eyes met the inclusion criterion. The mean pretreatment IOP was 38.7+/-11.9 mm Hg. The mean posttreatment IOP was 15.8+/-9.7 mm Hg. From life table analysis, the probability of having a posttreatment IOP of 21 mm Hg or less with or without medication was 70% at 1 year and 63% at 5 years. The probability of a graft remaining clear was 79% at 1 year and 56% at 5 years. In 85% of patients the visual acuity remained stable, in 11% the visual acuity improved, and in 4% the visual acuity deteriorated after **treatment**. One patient developed hypotony. Twenty patients (36.5%) were able to discontinue one or more glaucoma medications posttreatment. CONCLUSION: In this group of patients with PKP glaucoma, NCTY effectively lowered IOP over the long term, with 36.5% of patients discontinuing one or more glaucoma medications. There was, however, a significant incidence of graft failure at 5 years.

L26 ANSWER 22 OF 51 MEDLINE on STN
1999215794. PubMed ID: 10201611. Long-term results of **corneal graft survival** in infants and children with peters anomaly. Yang L L; Lambert S R; Lynn M J; Stulting R D. (Emory Eye Center, Emory University, Atlanta, Georgia 30322, USA.) Ophthalmology, (1999 Apr) 106 (4) 833-48. Journal code: 7802443. ISSN: 0161-6420. Pub. country: United States. Language: English.
AB OBJECTIVE: To determine the long-term results of **corneal graft survival** after penetrating keratoplasty for Peters anomaly and to identify risk factors for graft failure. DESIGN: Noncontrolled interventional case series: a single-center retrospective review of a consecutive surgical series. PARTICIPANTS: The records of all children 12 years of age or younger who underwent penetrating keratoplasty for Peters anomaly between January 1971 and December 1992 were reviewed. All study eyes had completed a minimum of 3 years of follow-up from the date of first keratoplasty and had undergone most of their corneal surgery at Emory University. INTERVENTION: Characteristics of the recipient, the eye, the donor, and the surgical procedure were analyzed for their influence on survival of the first graft. Survival probabilities were estimated using the Kaplan-Meier method. Multivariate regression analysis was performed to estimate relative risks and adjusted survival probabilities. MAIN OUTCOME MEASURE: Graft clarity. RESULTS: One hundred forty-four penetrating keratoplasties were performed in 72 eyes of 47 patients. The median age at first keratoplasty was 4.4 months. The median follow-up was 11.1 years. Fifty-four percent of eyes received one graft, 18% received two grafts, and 28% received three or more grafts. The overall probability of maintaining a clear first graft was 56% at 6 months, 49% at 12 months, 44% at 3 years, and 35% at 10 years. The probability of second or subsequent grafts surviving for 3 years was less than 10%. Thirty-nine percent of eyes had a clear graft at the time of review; 36% of eyes had a clear first graft. Multivariate analysis

was the most frequently identified cause of graft failure. Major complications after keratoplasty were phthisis, retinal detachment, cataract, and glaucoma. CONCLUSIONS: The overall long-term probability of maintaining a clear graft after initial penetrating keratoplasty for Peters anomaly is 35% +/- 0.06%, with subsequent grafts rarely surviving. Eyes with severe disease, larger donor corneas, coexisting central nervous system abnormalities, and anterior synechiae have significantly poorer outcomes than eyes without these factors. These data should be carefully considered before recommending corneal transplantation for Peters anomaly, particularly after previous graft failure.

L26 ANSWER 23 OF 51 MEDLINE on STN DUPLICATE 10
1999136648. PubMed ID: 9951497. Combined penetrating keratoplasty and trabeculectomy with mitomycin C. WuDunn D; Alfonso E; Palmberg P F. (Bascom Palmer Eye Institute, University of Miami School of Medicine, Florida, USA.) Ophthalmology, (1999 Feb) 106 (2) 396-400. Journal code: 7802443. ISSN: 0161-6420. Pub. country: United States. Language: English.
AB OBJECTIVE: To evaluate **corneal graft survival** and intraocular pressure control in eyes that have undergone combined penetrating keratoplasty and trabeculectomy with mitomycin C (MMC). DESIGN: Retrospective noncomparative case series. INTERVENTION: Penetrating keratoplasty combined with trabeculectomy with MMC and other surgical procedures. PARTICIPANTS: Twenty-four eyes of 22 patients undergoing combined penetrating keratoplasty and trabeculectomy with mitomycin C. MAIN OUTCOME MEASURES: Corneal graft clarity and intraocular pressure control. RESULTS: The cumulative probability of **corneal graft survival** was 85% at 1 year and 60% at 2 years. The cumulative probability of adequate pressure control was 67% at 3 months, 55% at 12 months, and 50% at 24 months. The incidence of bleb failure was higher in cases involving additional concomitant procedures, such as anterior vitrectomy, lens implantation or exchange, and drainage tube implantation. CONCLUSIONS: Combined penetrating keratoplasty and trabeculectomy with mitomycin C is associated with good **corneal graft survival** but also a risk of early failure of intraocular pressure control. Other concomitant procedures during the combined penetrating keratoplasty/trabeculectomy may increase the risk of early bleb failure.

L26 ANSWER 24 OF 51 MEDLINE on STN DUPLICATE 11
2000019764. PubMed ID: 10551999. Beneficial effect of preoperative mycophenolate mofetil in murine corneal transplantation. Reis A; Spelsberg H; Reinhard T; Braunstein S; Godehardt E; Sundmacher R. (Eye Clinic, Heinrich-Heine University, Moorenstr. 5, D-40 225 Duesseldorf, Germany.. reis@uni-duesseldorf.de) . Transplant international : official journal of the European Society for Organ Transplantation, (1999) 12 (5) 341-5. Journal code: 8908516. ISSN: 0934-0874. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB To investigate the effect of preoperative mycophenolate mofetil (MMF) on allograft survival in a murine corneal transplantation model. Corneal grafting was performed from Brown Norway to Lewis rats. Groups were divided as follows: Rats that received syngeneic or allogeneic grafts without therapy served as controls. MMF **treatment** was either started 7 days prior to transplantation and continued for 14 postoperative days (POD) or started at the day of corneal grafting until POD 14. MMF (20 mg/kg) administered postoperatively had no significant beneficial effect on **corneal graft survival** when compared with controls. However, the group receiving 40 mg/kg MMF

L26 ANSWER 25 OF 51 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1999:372138 Document No.: PREV199900372138. Long-term outcome of topical cyclosporine **treatment** following penetrating keratoplasty. Inoue, Kenji [Reprint author]; Amano, Shiro; Kimura, Chikako; Sato, Tsutomu; Fujita, Natsuya; Kagaya, Fumie; Kaji, Yuichi; Oshika, Tetsurou; Tsuru, Tadahiko; Araie, Makoto. Department of Ophthalmology, Branch Hospital, University of Tokyo School of Medicine, 3-28-6 Mejirodai, Bunkyo-ku, Tokyo, 112-8688, Japan. Nippon Ganka Gakkai Zasshi, (April, 1999) Vol. 103, No. 4, pp. 306-310. print.
CODEN: NGZAA6. ISSN: 0029-0203. Language: Japanese.

AB Purpose: To evaluate the long-term outcome of 2% topical cyclosporine A (CsA) **treatment** as an adjunct to topical corticosteroid in 86 eyes after penetrating keratoplasty (PK). Material and Methods: The subjects were 86 eyes of 83 patients who had undergone PK and received topical CsA **treatments**. Nighty-seven eyes of 95 patients who had undergone PK and received similar postoperative **treatments** except for topical CsA **treatments** served as control: The clinical outcome of PK was evaluated by rates of graft survival and rejection-free graft survival using Kaplan - Meier's method and compared with the log-rank test. The patients were subdivided into high-risk and low-risk groups. The high-risk patients were those who had corneal vascularization in 2 or more quadrants of the cornea preoperatively or who received regrafting. All other patients were assigned to the low-risk group. Thirty-six eyes of the CsA group and 50 eyes of the control group were high-risk cases. Results: In the high-risk patients, the rejection-free graft survival rate was 69.7% in the CsA group and 45.4% in the control group (p=0.030). However, there was no significant difference in the graft survival rate between the two groups. In the low-risk patients, there was no significant difference in the rates of rejection-free graft survival and graft survival between the CsA and the control group. Conclusion: 2% topical cyclosporine is effective in reducing the risk of allograft rejection in high-risk recipients.

L26 ANSWER 26 OF 51 MEDLINE on STN DUPLICATE 12
1999263058. PubMed ID: 10325545. Interleukin 10 **treatment** does not prolong experimental corneal allograft survival. Torres P F; de Vos A F; Martins B; Kijlstra A. (Department of Ophthalmology, Cornea Unit, Hospital Santo Antonio, University of Porto, Portugal.) Ophthalmic research, (1999) 31 (4) 297-303. Journal code: 0267442. ISSN: 0030-3747. Pub. country: Switzerland. Language: English.

AB In view of the known anti-inflammatory activities of interleukin (IL) 10, we investigated whether the administration of recombinant murine IL-10 prolonged **corneal graft survival**. A major histocompatibility complex mismatched rat model with AO rats as recipients of PVG donor corneas was used. A total of 39 corneal allografts was included in this study and divided into 7 groups for different **treatments**. Group I (n = 6), II (n = 8), III (n = 6) and IV (n = 7) were injected subconjunctivally with saline (control), 0. 5 ng, 5 ng or 50 ng of IL-10, respectively, on the day of transplantation and then on postoperative days (POD) 2, 4, 6, 8 and 10. Group V (n = 4) and group VI (n = 4) were injected intraperitoneally with saline (control) or 1 microg of IL-10, respectively, on the day before surgery, the day of grafting and then on POD 2, 4 and 6. Finally, group VII (n = 4) was injected with both subconjuctival 5 ng of IL-10 and intraperitoneal 1 microg of IL-10 on the same days as the previous groups. The median days for corneal rejection in the various groups were: group I, 11.3 +/- 0.9; group II, 11.5 +/- 0.9; group III, 11.6 +/- 0.8, and group IV, 10 +/- 1.0. Statistical analysis

L26 ANSWER 27 OF 51 MEDLINE on STN DUPLICATE 13
1998336664. PubMed ID: 9672793. Prolongation of corneal allograft survival by an interleukin-2-immunoglobulin fusion protein in mice. Zhang E P; Pohl T; Bulfone-Paus S; Wachtlin J; Kunzendorf U; Hoffmann F. (Department of Ophthalmology, Benjamin Franklin Medical Center, Free University of Berlin, Germany.) Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie, (1998 Jul) 236 (7) 486-92. Journal code: 8205248. ISSN: 0721-832X. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB BACKGROUND: Interleukin 2 (IL2) production by activated T-helper cells leads to activation and proliferation of cytotoxic T cells. Recently, an IL2-IgG fusion protein was found to suppress cell-mediated and humoral immune responses in mice. METHODS: We used the genetically engineered murine IL2-IgG2b fusion protein in a fully MHC-mismatched mouse keratoplasty model. The DTH reaction against sheep red blood cells was investigated as a measure of IL2-IgG2b-mediated immunosuppression. The animals were divided into three control groups (n > or = 6) [no **treatment**, subconjunctival (SQ) **treatment** with saline or mouse serum], two IL2 SQ-treated groups (14 micrograms or 140 micrograms), and four IL2-IgG2b-treated groups (14 micrograms, 140 micrograms or 280 micrograms SQ or 280 micrograms i.p.). RESULTS: Administration of 20 micrograms of IL2-IgG2b twice daily from the time of immunization until the time of challenge resulted in almost complete prevention of footpad swelling. The 140 micrograms SQ application of IL2 (allograft reaction on day 20.5 +/- 4.04) and the 280 micrograms SQ (day 19.2 +/- 2.48) or i.p. (day 19.7 +/- 1.5) application of IL2-IgG2b fusion protein significantly prolonged the **corneal graft survival** in comparison to the untreated group (day 13.4 +/- 1.35) ($P < 0.01$) or saline control group ($P < 0.01$) and the mouse-serum-treated group (day 14.7 +/- 3.5) ($P < 0.05$). CONCLUSION: Our results indicate that, at a total dose of 280 micrograms, the fusion protein IL2-IgG2b causes no detectable side effects and very effectively suppresses the immune response of the corneal allograft in mice. This fusion protein could prove useful in the **treatment** of allograft rejections and autoimmune diseases.

L26 ANSWER 28 OF 51 MEDLINE on STN DUPLICATE 14
1998146976. PubMed ID: 9486022. Influence of advanced recipient and donor age on the outcome of corneal transplantation. Australian Corneal Graft Registry. Williams K A; Muehlberg S M; Lewis R F; Coster D J. (Department of Ophthalmology, Flinders University of South Australia, Australia.) British journal of ophthalmology, (1997 Oct) 81 (10) 835-9. Journal code: 0421041. ISSN: 0007-1161. Pub. country: ENGLAND: United Kingdom. Language: English.

AB AIMS: The aims of this study were to examine the influence of advanced recipient and donor age on the long term outcome of corneal transplantation. METHODS: Records of 1036 penetrating corneal grafts in recipients aged > or = 80 years at surgery (defined as the elderly subset) and 8092 donor corneas used for transplantation were obtained from the Australian Corneal Graft Register database, Kaplan-Meier graft survival plots were compared using log rank statistics. RESULTS: Elderly recipients constituted 15% of the recipient pool. The major indication for corneal transplantation in the elderly was bullous keratopathy. Graft survival fell with increasing recipient age ($p < 0.00001$); the major cause of graft failure was rejection (33%). The desired outcome in 51% of cases was to improve vision and in 42% of cases to relieve pain; 23% of elderly recipients achieved a Snellen acuity of 6/18 or better in the grafted eye

recipients, but outcomes in terms of long term graft survival and visual rehabilitation were still good. Donor age did not affect graft survival.

L26 ANSWER 29 OF 51 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1998:128648 Document No.: PREV199800128648. Penetrating keratoplasty in the mentally retarded. McElvanney, A. M. [Reprint author]; Adhikary, H. P.. Eye Dep., Royal Surrey County Hosp., Egerton Road, Guildford, Surrey GU2 5XX, UK. Eye (London), (1997) Vol. 11, No. 6, pp. 786-789. print. ISSN: 0950-222X. Language: English.

AB Penetrating keratoplasty is infrequently performed in the mentally retarded due to the high risk of serious post-operative complications, in particular wound rupture and severe inflammation of the graft. Graft survival is hindered by the patient's tendency for eye rubbing and possibly self-inflicted injury. Adequate nursing support is essential to ensure strict compliance with post-operative **treatment**. A retrospective study of corneal graft outcomes in mentally retarded patients was undertaken to assess graft survival, visual rehabilitation, post-operative complications and the influence surgeon are presented. A continuous 10-0 nylon suture plasty performed in mentally retarded patients by one was employed in all cases. In 2 cases surgery was undertaken following perforation of the globe in patients with Down's syndrome. The grafts were retained in all cases and 2 patients achieved reasonably good acuity, although formal visual acuity assessment in these patients is limited. Penetrating keratoplasty in mentally retarded patients is a potentially hazardous procedure and patients require dose supervision and good support care. This series demonstrates that relatively successful outcomes can be obtained in some mentally retarded patients.

L26 ANSWER 30 OF 51 MEDLINE on STN DUPLICATE 15
96216041. PubMed ID: 8628559. Clinical and surgical factors influencing **corneal graft survival**, visual acuity, and astigmatism. Corneal Transplant Follow-up Study Collaborators. Vail A; Gore S M; Bradley B A; Easty D L; Rogers C A; Armitate W J. (Institute of Epidemiology and Health Services Research, University of Leeds, England.) Ophthalmology, (1996 Jan) 103 (1) 41-9. Journal code: 7802443. ISSN: 0161-6420. Pub. country: United States. Language: English.

AB PURPOSE: To quantify clinical and operative factors that influence corneal graft outcome. METHODS: A multifactorial analysis was done on 2242 corneal grafts registered by the United Kingdom Transplant Service from July 1987 to June 1991. RESULTS: There was an increased risk of graft failure in patients with preoperative diffuse and other noncentral stromal edema, less-common eye diseases, small trephine size, difference in donor and recipient sizes greater than 0.25 mm, and use of mixed continuous and interrupted sutures. Visual acuity 3 months after surgery was poorer in patients who had glaucoma and low visual acuity preoperatively, small trephine size, and combined vitreous surgery. Use of interrupted sutures resulted in higher astigmatism at 3 months. CONCLUSIONS: After allowing for the effects of recipient factors, surgical factors significantly affected corneal graft outcome. No factors that showed significant benefits for graft survival also adversely affected visual performance. Details of medical history, clinical condition, and surgical method failed to predict more than a small proportion of observed variability in visual performance of functioning grafts.

L26 ANSWER 31 OF 51 MEDLINE on STN DUPLICATE 16
96149280. PubMed ID: 8543073. Prevention of immune-mediated corneal graft

developed a corneal perforation in one eye requiring [illegible] keratoplasty. Nine consecutive corneal grafts were rapidly destroyed despite systemic immunosuppression with corticosteroid, cyclophosphamide, azathioprine and cyclosporin A. A rejection episode was observed in one graft before it melted and allograft rejection may have contributed to the destruction of other grafts. **Corneal graft survival** was ultimately achieved by systemic immunosuppression with the anti-lymphocyte monoclonal antibody, CAMPATH-1H. A single episode of rejection developed in the early post-operative period which was easily reversed by topical corticosteroid. Corneal melting has not recurred and the graft has now remained intact and clear for 24 months. Anti-lymphocyte monoclonal antibodies may therefore provide effective immunosuppression in the **treatment** of refractory ocular disorders.

L26 ANSWER 32 OF 51 MEDLINE on STN DUPLICATE 17

96014788. PubMed ID: 7556721. How successful is corneal transplantation? A report from the Australian Corneal Graft Register. Williams K A; Muehlberg S M; Lewis R F; Coster D J. (Department of Ophthalmology, Flinders University of South Australia, Adelaide.) Eye (London, England), (1995) 9 (Pt 2) 219-27. Journal code: 8703986. ISSN: 0950-222X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Corneal graft outcome was assessed within a large, prospectively collected database of 4499 records. Penetrating **corneal graft survival** was 91% at 1 year, 72% at 5 years and 69% at 7 years. The three most common indications for graft were keratoconus (30%), bullous keratopathy (25%) and failed previous graft (18%); the three most common causes of graft failure were rejection (34%), infection (18%) and glaucoma (9%). The vast majority of grafts were performed for improved visual acuity. About four-fifths of recipients achieved at least one line of better acuity on the Snellen chart post-operatively; of the remainder with unchanged or worse acuity, only 21% had failed grafts. Overall, 43% of recipients achieved a best corrected Snellen acuity of 6/12 or better, 52% achieved 6/18 or better, and 20% had acuitities of less than 6/60. Reasons for poor post-operative acuity (recorded as less than 6/60) included graft failure (41%) and comorbidities in the grafted eye (43%). A number of risk factors for graft failure were examined: in most instances, there was little room for decision-making or expert intervention.

L26 ANSWER 33 OF 51 MEDLINE on STN DUPLICATE 18

94321132. PubMed ID: 7913917. Effect of LFA-1 and ICAM-1 antibody **treatment** on murine corneal allograft survival. He Y; Mellon J; Apte R; Niederkorn J Y. (Department of Ophthalmology, University of Texas Southwestern Medical Center at Dallas 75235.) Investigative ophthalmology & visual science, (1994 Jul) 35 (8) 3218-25. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE. To examine the effect of anti-LFA-1 and anti-ICAM-1 antibody **treatment** on orthotopic **corneal graft survival** in a mouse model. METHODS. Anti-LFA-1 and anti-ICAM-1 antibodies were administered intraperitoneally before and shortly after orthotopic corneal transplantation. Grafts were observed by biomicroscopy, and survival times were determined. Cytotoxic T lymphocyte (CTL) and delayed-type hypersensitivity (DTH) responses to donor alloantigens were assessed at selected times after grafting. RESULTS. Administration of anti-LFA-1 antibody reduced the incidence of graft rejection from 90% in untreated donors to 47% in anti-LFA-1 treated mice.

immunized mice. CONCLUSIONS. Anti-ICAM-1 antibody does not promote graft survival even though it impairs CTL and DTH responses to donor alloantigens. By contrast, anti-LFA-1 antibody can significantly reduce the incidence of orthotopic corneal graft rejection and prevent the induction of normal allospecific CTL and DTH responses. Although anti-LFA-1 antibody is effective if given prophylactically, it is ineffective at preventing corneal graft rejection in previously immunized hosts.

L26 ANSWER 34 OF 51 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

94148626 EMBASE Document No.: 1994148626. Evidence that UV-B irradiation decreases corneal Langerhans cells and improves **corneal graft survival** in the rabbit. Hill J.C.; Sarvan J.; Maske R.; Els W.J.. Dept. of Ophthalmology, Medical School, University of Cape Town,Cape Town, South Africa. Transplantation 57/8 (1281-1284) 1994.
ISSN: 0041-1337. CODEN: TRPLAU. Pub. Country: United States. Language: English.

L26 ANSWER 35 OF 51 MEDLINE on STN DUPLICATE 19

95008811. PubMed ID: 7924332. Mixed lymphocyte culture responses in rabbits undergoing corneal grafting and topical cyclosporine **treatment.** Maske R; Hill J C; Horak S. (Department of Ophthalmology, Medical School, University of Cape Town, South Africa.) Cornea, (1994 Jul) 13 (4) 324-30. Journal code: 8216186. ISSN: 0277-3740. Pub. country: United States. Language: English.

AB Using a vascularized cornea rabbit model closely resembling human high-risk keratoplasty, corneal allografts were performed on three groups of animals that were paired and tested preoperatively by mixed lymphocyte cultures (MLCs). The three groups were group A, unmodified controls with clear corneas; group B, untreated animals with vascularized corneas; and group C, animals treated with topical cyclosporine (CSA) with vascularized corneas. The MLC results were expressed as stimulation indices (SIs) and divided into low (SI < or = 20) and high (SI > 20) responders and were correlated with final outcome of grafts using survival analysis estimates. In group A, five of 13 (38.5%) grafts rejected, the chance of failure depending on the degree of MLC mismatch between donor and recipient (p = 0.02). All allografts in group B rejected regardless of the degree of mismatch. In group C, seven of 12 (58.3%) grafts rejected, indicating that topical CSA significantly improved survival (p = 0.003) compared with group B. Grafts with mild degrees of MLC mismatch (low responders) survived better (p = 0.0003) than did higher degrees of MLC mismatch (high responders), all of which rejected despite **treatment.** Our results indicate that both corneal vascularization and the degree of donor-recipient matching play important roles in determining **corneal graft survival.**

L26 ANSWER 36 OF 51 MEDLINE on STN DUPLICATE 20

94306912. PubMed ID: 8033573. A prospective randomized trial of oral acyclovir after penetrating keratoplasty for herpes simplex keratitis. Barney N P; Foster C S. (Harvard Medical School, Boston, Massachusetts.) Cornea, (1994 May) 13 (3) 232-6. Journal code: 8216186. ISSN: 0277-3740. Pub. country: United States. Language: English.

AB **Corneal graft survival** in 13 patients (14 eyes) receiving oral acyclovir after penetrating keratoplasty for herpes simplex keratitis was compared with that in nine patients (nine eyes) who

($p < 0.01$). Graft failure occurred in 14% (2 of 14) of acyclovir-**treatment** eyes compared with 56% (five of nine) without acyclovir. Long-term prophylactic oral acyclovir significantly decreased the recurrence of herpes simplex keratitis and reduced corneal graft failure in patients who had a history of recurrent herpes simplex keratitis and who had undergone penetrating keratoplasty.

L26 ANSWER 37 OF 51 MEDLINE on STN

94134374. PubMed ID: 8302544. **Corneal graft survival** and visual outcome. A multicenter Study. Corneal Transplant Follow-up Study Collaborators. Vail A; Gore S M; Bradley B A; Easty D L; Rogers C A. (Department of Transplantation Sciences, Southmead Hospital, Bristol, England.) Ophthalmology, (1994 Jan) 101 (1) 120-7. Journal code: 7802443. ISSN: 0161-6420. Pub. country: United States. Language: English.

AB PURPOSE: The Corneal Transplant Follow-up Study has followed 2385 corneal transplants performed in the United Kingdom and the Republic of Ireland for up to 450 days to quantify factors influencing **corneal graft survival** and visual outcome 3 and 12 months postoperatively. METHODS: Multifactorial analyses of grafts registered by United Kingdom Transplant Support Service from July 1987 to June 1990 were used. Corrected visual acuity of functioning grafts was assessed at 3 and 12 months. RESULTS: Of 2385 corneal transplants followed, 214 failures were observed: graft survival was 95% at 3 months and 89% at 1 year. Similar factors affected outcome at each time. Decreased risk of failure was associated with surgeons reporting most grafts, and increased risk was associated with regrafts, patients younger than 10 years of age, nonvisual reasons for grafting, endothelial failure, and deep vascularization. Visual outcome was worse in older patients and was associated with cosmetic reasons for grafting, superficial vascularization preoperatively, and secondary endothelial failure. Visual acuity was better when the other eye had been grafted previously, or when the diagnosis was keratoconus or stromal dystrophy. CONCLUSIONS: Primary endothelial failure was associated with high failure rates but good visual results when functioning. Most other factors had similar effects on both outcome measures. Improved outcome under highest-reporting surgeons was slight, and indicated possible differences in postoperative care.

L26 ANSWER 38 OF 51 EMBASE on STN

93206491 EMBASE Document No.: 1993206491. Effects of the immunosuppressant FK506 on a penetrating keratoplasty rejection model in the rat. Nishi M.; Herbort C.P.; Matsubara M.; Morishita Y.; Nishimura M.; Nieda M.; Mori S.; Mochizuki M.. Escola Paulista de Medicina, Rua Botucatu 820, Vila Clementino,SP CEP 04038 Sao Paulo, Brazil. Investigative Ophthalmology and Visual Science 34/8 (2477-2486) 1993.
ISSN: 0146-0404. CODEN: IOVSDA. Pub. Country: United States. Language: English. Summary Language: English.

AB Purpose. The immunosuppressive effects of FK506 on allogeneic corneal transplantation were tested in a rat model. Methods. Inbred-strain Lewis rats were used as recipients, and Fisher rats were used as donors. Intraperitoneal injection of FK506 (0.3, 1.0, and 3.0 mg/kg per day) was administered for 2 weeks, and the grafts were inspected by clinical evaluation. Mixed lymphocyte culture assay, using lymphocytes from recipients of penetrating keratoplasty as responder cells and irradiated splenocytes from naive Fisher or Brown Norway as stimulator cells, was used to identify allogeneic stimulation. The rejection process was studied

Fisher stimulator splenocytes. FK506 suppressed this primed lymphocyte proliferation. Immunohistochemical and histologic studies confirmed the clinical evaluations. Untreated rat corneas, at the second postoperative week, presented a large number of helper/inducer T cells, macrophages, IL-2 receptor-expressing cells and Ia-antigen-expressing cells. In the same period, FK506-treated rats appeared normal and had no cellular infiltration. Corneas rejected after FK506 cessation had less intense cell infiltration than the control corneas. Conclusions. These data indicate that FK506 prolonged the **corneal graft survival** and can be a potentially useful drug in the immunotherapeutic arsenal to suppress corneal graft rejection.

L26 ANSWER 39 OF 51 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

93082584 EMBASE Document No.: 1993082584. Effect of monoclonal antibody on **corneal graft survival** across major and minor histocompatibility mismatches. Duguid I.G.M.; Koulmanda M.; Mandel T.E.. Transplantation Unit, Walter and Eliza Hall Institute, Royal Melbourne Hospital,Parkville, Vic. 3050, Australia. Transplantation Proceedings 25/1 (844) 1993.
ISSN: 0041-1345. CODEN: TRPPA8. Pub. Country: United States. Language: English.

L26 ANSWER 40 OF 51 MEDLINE on STN

93905511. PubMed ID: 10148869. Storage, surgery, outcome, and complications of corneal and conjunctival grafts. Williams K A; Davis G J; Coster D J. (Flinders Medical Center, Adelaide, Australia.) Current opinion in ophthalmology, (1993 Aug) 4 (4) 75-83. Ref: 71. Journal code: 9011108. ISSN: 1040-8738. Pub. country: United States. Language: English.

AB Corneal transplantation is still limited by a shortage of donor material, but the type of storage medium used once a cornea has been acquired is probably irrelevant to graft outcome. Vancomycin HCl shows promise as a supplement to gentamicin sulfate in storage media. New methods of HLA typing using donor ocular tissue have largely helped to overcome the problems associated with typing of cadaveric blood, but the value of HLA typing in improving **corneal graft survival** is now in doubt. Alternative regimens of immunosuppression are being tested in animal models, but there is still no consensus on the best ways to use existing agents such as corticosteroids. Rejection remains the most common cause of unsuccessful corneal grafting in large cohorts, but glaucoma and astigmatism also limit postoperative graft function. Limbal stem cell grafts are promising for the management of many ocular surface diseases and conjunctival limbal autografts for pterygia may be the most successful surgical method for preventing recurrence.

L26 ANSWER 41 OF 51 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

92255492 EMBASE Document No.: 1992255492. Site-specific immunosuppression for **corneal graft survival** in the rat. Katami M.; White D.J.G.; Watson P.G.. Department of Ophthalmology, School of Medicine, Kitasato University, 1-15-1 Kitasato,Sagamihara, Kanagawa 228, Japan. Transplantation Proceedings 24/4 (1406-1408) 1992.
ISSN: 0041-1345. CODEN: TRPPA8. Pub. Country: United States. Language: English.

L26 ANSWER 42 OF 51 MEDLINE on STN DUPLICATE 21

93041587. PubMed ID: 1358194. Prolongation of rat **corneal**

AB A rat model of orthotopic corneal graft rejection was used to investigate the effect of depletion of subpopulations of immune cells by **treatment** with monoclonal antibodies. Though CD4+ cells were not eliminated completely by anti-CD4 monoclonal antibodies there was a profound delay in the rejection times of orthotopic corneal allografts. Furthermore a third of the CD4+ depleted animals failed to reject corneal allografts by 100 days post grafting. Despite an almost complete depletion of circulating CD8+ cells, the anti-CD8 antibody treated animals rejected corneal allografts in a similar time course to allografted controls treated with a non-reactive control antibody OX21. These results demonstrate that CD8+ T-cells are not required for rejection of corneal allografts whereas CD4+ T-cells play a critical role in the rejection response. **Treatment** with anti-CD4 antibodies may have a useful clinical application.

L26 ANSWER 43 OF 51 MEDLINE on STN
93002857. PubMed ID: 1390530. Long-term survival of endothelium following transplantation of corneas stored by organ culture. Redmond R M; Armitage W J; Whittle J; Moss S J; Easty D L. (Department of Ophthalmology, Bristol University.) British journal of ophthalmology, (1992 Aug) 76 (8) 479-81. Journal code: 0421041. ISSN: 0007-1161. Pub. country: ENGLAND: United Kingdom. Language: English.

AB This study reports **corneal graft survival,** endothelial cell changes, and visual outcome in 20 patients who received some of the first corneas stored by organ culture in the Corneal Transplant Service Eye Bank in Bristol. Mean donor age was 48 years (SD 15, n = 20) and corneas were stored for an average of 21 days (SD 7, n = 20). Preoperative endothelial cell density was 2334 cells/mm2 (SD 235, n = 18) and this fell by 8% (SD 12) to 2158 cells/mm2 (SD 372) within the first 2 months following transplantation. In 13 patients, endothelial cell density thereafter declined exponentially with a half-life of 41 months (SD 17, n = 12; one patient excluded as an outlier). Corneas that suffered rejection episodes showed the highest rates of loss of endothelial cells. Endothelial cell loss 4 years after transplantation was 46% (SD 16, n = 12), which was similar to the postoperative decline in cell density reported for corneas stored for far shorter periods in McCarey-Kaufman medium at 4 degrees C.

L26 ANSWER 44 OF 51 MEDLINE on STN DUPLICATE 22
93114226. PubMed ID: 1473452. Systemic acyclovir and penetrating keratoplasty for herpes simplex keratitis. Foster C S; Barney N P. (Immunology Service, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston.) Documenta ophthalmologica. Advances in ophthalmology, (1992) 80 (4) 363-9. Journal code: 0370667. ISSN: 0012-4486. Pub. country: Netherlands. Language: English.

AB **Corneal graft survival** in 13 patients (14 eyes) receiving oral acyclovir following corneal transplantation for herpes simplex keratitis was compared to that in nine patients (9 eyes) who underwent penetrating keratoplasty for herpes simplex keratitis without receiving postoperative acyclovir. Mean age, duration of disease, and time of follow-up did not differ in the two groups. There were no recurrences of herpes simplex keratitis in any patient receiving acyclovir during a mean follow-up of 16.5 months compared to a 44% (4/9) recurrence rate in patients without acyclovir during a mean follow-up of 20.6 months ($p < 0.01$). Graft failure occurred in 14% (2/14) of acyclovir **treatment** eyes and in 56% (5/9) of the grafts in patients not receiving acyclovir. Long term prophylactic oral acyclovir significantly

THERAPY IN PREVENTION OF CORNEAL GRAFT REJECTION. ANGELERI M B [reprint author]; CREMONTE L G. DIV OCULISTICA, OSPEDALE CIVILE DI TORTONA. Archivio di Medicina Interna, (1992) Vol. 43, No. 2, pp. 81-85. ISSN: 0004-010X. Language: ITALIAN.

AB This work examines the newest results in preventive **treatment** of corneal graft rejection. In particular, immunodepressive therapy and new drugs, which while not of great value against graft rejection, still facilitate **corneal graft survival**.

L26 ANSWER 46 OF 51 MEDLINE on STN DUPLICATE 23

92050662. PubMed ID: 1945292. Azathioprine and cytarabine applied topically prolong **corneal graft survival** in rabbits. Golubovic S. (University Eye Clinic, Medical Faculty, Belgrade, Yugoslavia.) Ophthalmic research, (1991) 23 (4) 213-9. Journal code: 0267442. ISSN: 0030-3747. Pub. country: Switzerland. Language: English.

AB Azathioprine and cytarabine applied topically as 0.1% solution in the grafted rabbit eye significantly prolong corneal allograft survival time. Mean **corneal graft survival** time was 61 +/- 27.76 days and 55 +/- 26.79 days in the group treated with azathioprine and cytarabine, respectively, while mean **corneal graft survival** time in the control group of rabbits with no immunosuppressive therapy was 19 +/- 4.47 days. After completion of the immunosuppressive **treatment**, the achieved azathioprine effect lasted longer than the cytarabine effect. Favourable azathioprine and cytarabine effects on corneal allograft survival in rabbits were obtained with no serious local and systemic side effects. Only moderate hyperemia of the palpebral and bulbar conjunctiva was recorded during the first days of **treatment**. No other side effects were observed.

L26 ANSWER 47 OF 51 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

91:516584 The Genuine Article (R) Number: GF072. AZATHIOPRINE AND CYTARABINE APPLIED TOPICALLY PROLONG **CORNEAL GRAFT-SURVIVAL** IN RABBITS. GOLUBOVIC S (Reprint). UNIV BELGRADE, FAC MED, EYE CLIN, PASTEROVA 2, YU-11000 BELGRADE, YUGOSLAVIA (Reprint). OPHTHALMIC RESEARCH (1991) Vol. 23, No. 4, pp. 213-219. Pub. country: YUGOSLAVIA. Language: ENGLISH.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Azathioprine and cytarabine applied topically as 0.1% solution in the grafted rabbit eye significantly prolong corneal allograft survival time. Mean **corneal graft survival** time was 61 +/- 27.76 days and 55 +/- 26.79 days in the group treated with azathioprine and cytarabine, respectively, while mean **corneal graft survival** time in the control group of rabbits with no immunosuppressive therapy was 19 +/- 4.47 days. After completion of the immunosuppressive **treatment**, the achieved azathioprine effect lasted longer than the cytarabine effect. Favourable azathioprine and cytarabine effects on corneal allograft survival in rabbits were obtained with no serious local and systemic side effects. Only moderate hyperemia of the palpebral and bulbar conjunctiva was recorded during the first days of **treatment**. No other side effects were observed.

L26 ANSWER 48 OF 51 MEDLINE on STN DUPLICATE 24

88297197. PubMed ID: 3042525. Increase of **corneal graft survival** by use of topically immunosuppressive agents in rabbits. Golubovic S; Radmanovic B Z. (University Eye Clinic, Medical Faculty, Belgrade, Yugoslavia.) Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und

(0.1% in arachis oil) applied four times daily for 4 weeks. A control group of animals was treated with dexamethasone in the same way. The mean graft survival time was 52 +/- 18.5 days in the group treated with dexamethasone and 80 +/- 18.2 and 73 +/- 23.5, respectively, in the groups treated with cyclophosphamide and methotrexate. Cyclophosphamide and methotrexate applied topically produced no systemic side effects, and only one mild and transient local side effect in the form of hyperemia of the bulbar and palpebral conjunctiva. These two immunosuppressive drugs were more effective than the corticosteroid currently in clinical use, i.e., dexamethasone.

L26 ANSWER 49 OF 51 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

83094079 EMBASE Document No.: 1983094079. [Effect of local administration of cyclosporin A on **corneal graft survival** in the rabbit]. DER EFFEKT DER LOKALEN GABE VON CYCLOSPORIN A AUF DIE UBERLEBENSZEIT VON HORNHAUTTRANSPLANTATEN BEIM KANINCHEN. Kana J.S.; Hoffmann F.; Buchen R.; et al.. Inst. Klin. Physiol., Klin. Steglitz, Freie Univ. Berlin, D-1000 Berlin 45, Germany. Fortschritte der Ophthalmologie 79/2 (132-134) 1982.
CODEN: FORODD. Pub. Country: Germany. Language: German. Summary Language: English.

AB The skin graft-induced rejection of corneal allografts in rabbits was delayed by cyclosporin A (CS-A) applied locally to the eye. The subconjunctival application of CS-A (3 mg/kg/day) was irritating whereas the topical instillation of 5% water-soluble CS-A eye drops was well tolerated. The corneal grafts were rejected after discontinuation of the therapy. Rejection was confirmed by scanning and transmission electron microscopy. A local immunosuppressive and/or anti-inflammatory effect of topical CS-A is postulated.

L26 ANSWER 50 OF 51 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 25

83022502 EMBASE Document No.: 1983022502. Prolonged **corneal graft survival** using topically applied cyclosporin A. Hunter P.A.; Rice N.S.C.; Jones B.R.. Inst. Ophthalmol., London, United Kingdom. Transactions of the Ophthalmological Societies of the United Kingdom 102/1 (19-20) 1982.
CODEN: TOSUAH. Pub. Country: United Kingdom. Language: English.

AB The immunosuppressive cyclosporin A was applied topically to the recipient eye in a rabbit model of corneal allograft rejection. When **treatment** was continued for 13 weeks, 44 per cent of allografts failed to develop signs of rejection six months after surgery. Revascularization of the surviving allografts induced typical signs of allograft rejection suggesting that the prolonged survival was the result of vessel regression rather than specific immunological tolerance.

L26 ANSWER 51 OF 51 MEDLINE on STN DUPLICATE 26

82070923. PubMed ID: 7030537. Cyclosporin A applied topically to the recipient eye inhibits corneal graft rejection. Hunter P A; Wilhelmus K R; Rice N S; Jones B R. Clinical and experimental immunology, (1981 Jul) 45 (1) 173-7. Journal code: 0057202. ISSN: 0009-9104. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Corneal graft survival** in rabbits was significantly (P less than 0 . 001) prolonged by topical **treatment** to the recipient eye with cyclosporin A 1% in arachis oil applied five times daily for 4 weeks. No graft was rejected whilst **treatment**

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=> s (DeVries g?/au)
L27         984 (DEVRIES G?/AU)

=> s l27 and VEGFR3
L28           0 L27 AND VEGFR3

=> s l27 and corneal graft
L29           0 L27 AND CORNEAL GRAFT

=> s l27 and tyrosine kinase inhibitor
L30           0 L27 AND TYROSINE KINASE INHIBITOR

=> s l27 and "MAE87"
L31           0 L27 AND "MAE87"

=> s l27 and treatment
L32         103 L27 AND TREATMENT

=> s l32 and transplant
L33           0 L32 AND TRANSPLANT

=> s l32 and "MAE106"
L34           0 L32 AND "MAE106"

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L35  ANSWER 1 OF 50     MEDLINE on STN
2004148596.    PubMed ID: 15042580.   Prostaglandin E2 and 6-keto-prostaglandin
     F1alpha production is elevated following traumatic injury to sciatic nerve
     dagger. Muja Naser; DeVries George H. (Neuroscience Graduate
     Program, Neurobiology, and Anatomy Loyola University of Chicago, Maywood,
     Illinois. ) Glia, (2004 Apr 15) 46 (2) 116-29.  Journal code: 8806785.
     ISSN: 0894-1491. Pub. country: United States. Language: English.
AB   Sciatic nerve explants cultured either alone or in the presence of
     peritoneal macrophages were used to study prostaglandin E(2) (PGE(2)) and
     6-keto-PGF(1alpha) production following traumatic peripheral nerve injury.
     Although barely detectable at early time points (1-3 h in vitro), the
     production of PGE(2) and 6-keto-PGF(1alpha) by sciatic nerve explants
     increased significantly after 18 h and remained elevated for up to 96 h.
     The cyclooxygenase-2 (COX-2) selective inhibitor, NS-398, inhibited PGE(2)
     and 6-keto-PGF(1alpha) production by injured sciatic nerve in a
     dose-dependent manner.  Consistent with the observed effect of NS-398,
     peripheral nerve explants, as well as Schwann cells and perineural
     fibroblasts cultured from neonatal sciatic nerve, each contained COX-2
     immunoreactivity after 24 h in vitro.  Both Schwann cells and perineural
     fibroblasts produced significant amounts of PGE(2) and 6-keto-PGF(1alpha);
     but only in the presence of arachidonic acid.  As observed for injured
     sciatic nerve, the production of PGE(2) and 6-keto-PGF(1alpha) by primary
     Schwann cells and perineural fibroblasts was completely inhibited by
     NS-398.  Compared to macrophages cultured alone, macrophages cultured in
     the presence of sciatic nerve explants produced large amounts of PGE(2),
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response to soluble factors produced by injured nerve but not during the phagocytosis of peripheral nerve debris. Published 2004 Wiley-Liss, Inc.

=> s l35 and "deVries Gerald"
L36 0 L35 AND "DEVRIES GERALD"

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L35 ANSWER 1 OF 50 MEDLINE on STN
2004148596. PubMed ID: 15042580. Prostaglandin E2 and 6-keto-prostaglandin F1alpha production is elevated following traumatic injury to sciatic nerve dagger. Muja Naser; **DeVries George H.** (Neuroscience Graduate Program, Neurobiology, and Anatomy Loyola University of Chicago, Maywood, Illinois.) Glia, (2004 Apr 15) 46 (2) 116-29. Journal code: 8806785. ISSN: 0894-1491. Pub. country: United States. Language: English.
AB Sciatic nerve explants cultured either alone or in the presence of peritoneal macrophages were used to study prostaglandin E(2) (PGE(2)) and 6-keto-PGF(1alpha) production following traumatic peripheral nerve injury. Although barely detectable at early time points (1-3 h in vitro), the production of PGE(2) and 6-keto-PGF(1alpha) by sciatic nerve explants increased significantly after 18 h and remained elevated for up to 96 h. The cyclooxygenase-2 (COX-2) selective inhibitor, NS-398, inhibited PGE(2) and 6-keto-PGF(1alpha) production by injured sciatic nerve in a dose-dependent manner. Consistent with the observed effect of NS-398, peripheral nerve explants, as well as Schwann cells and perineural fibroblasts cultured from neonatal sciatic nerve, each contained COX-2 immunoreactivity after 24 h in vitro. Both Schwann cells and perineural fibroblasts produced significant amounts of PGE(2) and 6-keto-PGF(1alpha); but only in the presence of arachidonic acid. As observed for injured sciatic nerve, the production of PGE(2) and 6-keto-PGF(1alpha) by primary Schwann cells and perineural fibroblasts was completely inhibited by NS-398. Compared to macrophages cultured alone, macrophages cultured in the presence of sciatic nerve explants produced large amounts of PGE(2), whereas the level of 6-keto-PGF(1alpha) was unchanged. In contrast, macrophages treated with adult sciatic nerve homogenate did not produce significant amounts of either PGE(2) or 6-keto-PGF(1alpha) during the entire course of **treatment**. We conclude that injured sciatic nerves produce PGE(2) and 6-keto-PGF(1alpha) by a mechanism involving COX-2 activity and that macrophages produce large amounts of PGE(2) in response to soluble factors produced by injured nerve but not during the phagocytosis of peripheral nerve debris. Published 2004 Wiley-Liss, Inc.

L35 ANSWER 2 OF 50 MEDLINE on STN DUPLICATE 1
2002738337. PubMed ID: 12499280. SPARC is a key Schwannian-derived inhibitor controlling neuroblastoma tumor angiogenesis. Chlenski Alexandre; Liu Shuqing; Crawford Susan E; Volpert Olga V; **DeVries George H**; Evangelista Amy; Yang Qiwei; Salwen Helen R; Farrer Robert; Bray James; Cohn Susan L. (The Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Feinberg School of Medicine, Chicago, Illinois 60611, USA.) Cancer research, (2002 Dec 15) 62 (24) 7357-63. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.
AB Neuroblastoma (NB), a common pediatric neoplasm, consists of two main cell populations: neuroblastic/ganglionic cells and Schwann cells. NB tumors with abundant Schwannian stroma display a more benign clinical behavior than stroma-poor tumors. Recent studies suggest that Schwann cells

protein acidic and rich in cysteine), an extracellular matrix protein. We found SPARC to be critical for the antiangiogenic phenotype of cultured Schwann cells. We also show that purified SPARC potently inhibits angiogenesis and significantly impairs NB tumor growth in vivo. SPARC may be an effective candidate for the **treatment** of children with clinically aggressive, Schwannian stroma-poor NB tumors.

L35 ANSWER 3 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2003:154944 Document No.: PREV200300154944. Time Course of Retinal Edema Following Verteporfin Photodynamic Therapy (PDT) in Pigmented Rabbits: An Optical Coherence Tomography (OCT), Color Funduscopy and NaF Angiography Study. Burke, J. A. [Reprint Author]; Lin, T. [Reprint Author]; Ho, W. [Reprint Author]; **DeVries, G.** [Reprint Author]; Wheeler, L. [Reprint Author]. Biological Sciences, Allergan, Inc., Irvine, CA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 2824. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: To investigate the effects of verteporfin PDT on retinal mophology in the normal rabbit. Methods: Conscious pigmented rabbits were given an iv infusion of 10 mls (1 ml/min) verteporfin 0.2 mg/kg (equivalent to clinical dose by body weight) via the marginal ear vein. Animals were dilated with phenyephrine and tropicamide, anesthetized with iv ketamine and acepromazine, and irradiated in the lower fundus with a 689 nm diode laser at 50 J/cm2, 600 mW/cm2 according to the following study designs. Study 1: Single 5 mm spot 3 minutes post-verteporfin. Follow-up measurements (color funduscopy and NaF angiography with a Zeiss FF 450 IR fundus camera and OCT with a Zeiss Humphrey OCTII system) were made on Days 1, 2, 4, 7, 9, 11, 14, 16 and 18. Study 2: Two 1.5 mm spots at 10 and 15 minutes post-PDT placed 6 mm apart. Follow-up measurements as above were made at 4 hours, and Days 1, 2, 3 and 4 post-PDT. Results: Study 1: Retinal thickness (RPE - ILM) was maximal on Day 4: 524 +- 10 um including a subretinal cyst of 292 +- 17 um (normal thickness = 156 +- 1.4 um) which resolved by Day 7. Retinal thickness was significantly elevated up to Day 9. Maximum area of NaF hypofluorescence within the PDT lesion occurred at Day 4 (16 +- 1 mm2 out of a possible 19.6 mm2 compared to hypofluorescence area in untreated retina of 0.17 +- 0.1 mm2). Study 2: Retinal thickness in the 10-minute lesion was greater than in the 15-minute lesion up to Day 2. The peak difference occurred at Day 1; retinal thickness for the 10-minute lesion was 257 +- 6 um (including a subretinal cyst of 76.4 +- 5.3 um) and for the 15-minute lesion was 196 +- 9 um. Hypofluorescence in these smaller (1.5 mm) lesions was obscured by the edema which spread beyond the borders of the **treatment** area in the 10-minute lesion; color funduscopy showed that edema area increased up to Day 3; maximum increase was 13.6 +- 0.9 mm2 @ Day 2. Conclusion: Verteporfin PDT produces edema, which increases retinal thickness, including subretinal cysts, in the normal rabbit fundus. These effects were transient, resolving in just over a week.

L35 ANSWER 4 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2002:3979 Document No.: PREV200200003979. Axons and O2A progenitors communicate with each other through the release of soluble factors. **DeVries, G. H.** [Reprint author]; Raabe, T. D.; Andrews, E. M. [Reprint author]; Scharnweber, R.; Farrer, R. G.. Cell Biol, Neurobiol and Anat, Loyola University, Maywood, IL, USA. Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2388. print.

membranes and used them to treat oligodendrocyte progenitor (O2A) cells in culture to study how the O2A cells responded to axolemma with respect to intracellular signaling and proliferation. **Treatment** of O2A cells with axolemma induced a sustained (up to 2 hours) activation of MAP kinase. This response was not contact-dependent, since membranes added to the culture medium, but separated from the cells by a 0.02 mm membrane insert, also induced MAP kinase activation. Furthermore, MAP kinase activity was stimulated by medium that had been conditioned first by O2A cells, then with axolemma, but no activity was induced with O2A conditioned medium itself or with medium conditioned with axolemma alone. Proliferation of the O2A cells increased in a dose-dependent manner in response to increasing concentrations of axolemma when compared to liver microsome controls. In addition, O2A-conditioned medium that was boiled first then treated with axolemma showed no effect on proliferation, suggesting that a soluble factor released by the O2A cells was heat labile. These results demonstrate that O2A cells and axolemmal membranes communicate with each other through the release of soluble factors which activate intracellular signaling pathways within the O2A progenitors.

L35 ANSWER 5 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2002:3972 Document No.: PREV200200003972. Elevated prostaglandin release from degenerating sciatic nerve explants: Contribution of cyclooxygenase 2.
Muja, N. [Reprint author]; **DeVries, G. H.** [Reprint author].
Neuroscience Program, Loyola University of Chicago, Maywood, IL, USA.
Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2387.
print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295. Language: English.

AB Schwann cells express prostanoid receptors coupled to the cAMP mediated signaling cascade. To identify physiologic sources of prostanoids for Schwann cells, we determined the extent of prostaglandin release from explants of sciatic nerve. PGE2 and PGI2 levels in the conditioned medium of sciatic nerve explants increased rapidly between 18 and 24 hours and remained elevated for up to 96 hours. Medium from primary Schwann cells and perineural fibroblasts treated with arachidonic acid (0.001-1 muM) also contained significant levels of both PGE2 and PGI2. The production of PGE2 and PGI2 by sciatic nerve explants and primary cultured cells was inhibited by the COX-2 specific inhibitor NS-398 (EC50=5 nM). Compared to medium from quiescent macrophages, medium from macrophages cultured in the presence of adult sciatic nerve explants contained significant amounts of PGE2 whereas the level of PGI2 production was not changed. Similar trends in PGE2 and PGI2 production were observed following **treatment** of cultured macrophages with conditioned medium from either primary Schwann cells or perineural fibroblasts. In contrast, macrophages treated with a homogenate of adult sciatic nerve (1-25 mug/ml) did not produce significant levels of either PGE2 or PGI2 over the entire course of **treatment**. We conclude that Schwann cells and perineural fibroblasts are significant physiologic sources of prostanoids within 24 hours of traumatic peripheral nerve injury and that recruited macrophages may be a secondary source of prostanoids, particularly PGE2, at the injury site.

L35 ANSWER 6 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:547205 Document No.: PREV200100547205. Activated microglia secrete neuregulins. Deadwyler, G. D. [Reprint author]; Tsai, S. Y. [Reprint author]; **DeVries, G. H.** [Reprint author]. Research Service,

survival, proliferation and differentiation of neural cells via activation of erbB receptors. To date, astrocytes and oligodendrocytes have been shown to contain and secrete NRGs. Our previous results showed that NRGs was upregulated in the brains of rats with permanent middle cerebral artery occlusion (MCAO), which is an experimental stroke model. Since microglia are activated after neural injury, we hypothesize that activated microglia could secrete NRGs. Primary microglia were isolated from mixed glial cultures by the method of McCarthy and de Vellis. Unstimulated microglia cultures were 99% pure as determined by ED1 staining. These microglia showed weak immunoreactivity for NRG-alpha only. Activation by LPS (.5 microgram/ml) for 2 hours did not appreciably increase NRG-alpha immunoreactivity. However, LPS **treatment** resulted in the secretion of apprx70kDa NRG-alpha isoform in the microglia medium conditioned for 2hours. Neuregulin-beta was not detected in the microglia by immunocytochemistry or in the conditioned medium by Western blot at any time. The secretion of NRG-alpha by activated microglia is consistent with the NRGs observed in the rat MCAO model, which consists of NRG-alpha only. These results support the hypothesis that activated microglia secrete NRGs to promote neuronal recovery after brain injury.

L35 ANSWER 7 OF 50 MEDLINE on STN DUPLICATE 2
2001453679. PubMed ID: 11483647. Identification and functional characterization of thromboxane A2 receptors in Schwann cells. Muja N; Blackman S C; Le Breton G C; **DeVries G H.** (Neuroscience Graduate Program, and Department of Cell Biology, Neurobiology and Anatomy, Loyola University of Chicago, Maywood, Illinois, USA.) Journal of neurochemistry, (2001 Aug) 78 (3) 446-56. Journal code: 2985190R. ISSN: 0022-3042. Pub. country: United States. Language: English.

AB Previous reports have demonstrated the presence of functional thromboxane A2 (TP) receptors in astrocytes and oligodendrocytes. In these experiments, the presence and function of TP receptors in primary rat Schwann cells (rSC) and a neurofibrosarcoma-derived human Schwann cell line (T265) was investigated. Immunocytochemical and immunoblot analyses using polyclonal anti-TP receptor antibodies demonstrate that both cell types express TP receptors. **Treatment** with the stable thromboxane A2 mimetic U46619 (10 microM) did not stimulate intracellular calcium mobilization in rSC, whereas T265 cells demonstrated a calcium response that was inhibited by prior **treatment** with TP receptor antagonists. U46619 also stimulated CREB phosphorylation on Ser133 in T265 cells and, to a lesser extent, in rSC. To identify potential mechanisms of CREB phosphorylation in rSC, we monitored intracellular cAMP levels following U46619 stimulation. Elevated levels of cAMP were detected in both rSC (20-fold) and T265 (15-fold) cells. These results demonstrate that TP receptor activation specifically stimulates CREB phosphorylation in T265 cells, possibly by a calcium- and/or cAMP-dependent mechanism. In contrast, TP receptor activation in rSC stimulates increases in cAMP and CREB phosphorylation but does not elicit changes in intracellular calcium.

L35 ANSWER 8 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:487290 Document No.: PREV200100487290. Axonal control of angiogenesis in normal and Neurofibromatosis Type-1 derived Schwann cells. Lertsburapa, T. [Reprint author]; McNulty, J. A. [Reprint author]; Nahas, S. L.; **DeVries, G. H.** [Reprint author]. Cell Biology, Neurobiology and Anatomy, Loyola University Medical Center, Maywood, IL, USA. Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 412. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San

control the expression of factors secreted by SC, we hypothesize that axonal contact modulates angiogenic and anti-angiogenic factor secretion by SC. This study determined if two angiogenic factors, Vascular Endothelial Growth Factor (VEGF) and Platelet Derived Growth Factor (PDGF), and an anti-angiogenic factor, Pigment Epithelium Derived Factor (PEDF), were modulated by axonal contact. Using RT-PCR, Western blot and immunocytochemistry, we found that VEGF and PEDF are expressed and secreted by normal and NF1-derived SC. NF1 SC CM stimulated endothelial cell proliferation and migration; VEGF neutralization Ab significantly decreased both activities. Using an in vitro model of axonal contact (addition of axolemma enriched fraction (AEF)), we observed the down regulation of PEDF and the upregulation of PDGFAA and PDGFBB in normal SC. However, **treatment** of NF1-derived SC with AEF had no effect on the secretion of PEDF levels as determined by Western blot analysis of CM. Our results indicate that axonal contact modulates expression of angiogenic and anti-angiogenic factors in normal SC but this may not hold true for transformed cells.

L35 ANSWER 9 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:290618 The Genuine Article (R) Number: 301UQ. One year growth hormone replacement therapy does not alter colonic epithelial cell proliferation in growth hormone deficient adults. Beentjes J A M (Reprint); vanGorkom B A P; Sluiter W J; **deVries G E**; Kleibeuker J H; Dullaart R P F. UNIV GRONINGEN HOSP, DEPT INTERNAL MED, DIV ENDOCRINOL, POB 30-001, NL-9700 RB GRONINGEN, NETHERLANDS (Reprint); UNIV GRONINGEN HOSP, DIV GASTROENTEROL, NL-9700 RB GRONINGEN, NETHERLANDS; UNIV GRONINGEN HOSP, DIV MED ONCOL, NL-9700 RB GRONINGEN, NETHERLANDS. CLINICAL ENDOCRINOLOGY (APR 2000) Vol. 52, No. 4, pp. 457-462. Publisher: BLACKWELL SCIENCE LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0300-0664. Pub. country: NETHERLANDS. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB OBJECTIVE Increased colonic epithelial cell proliferation has been found in various conditions associated with increased risk of colorectal cancer including acromegaly. In a placebo-controlled study we determined the effect of growth hormone (GH) replacement therapy in GH deficient adults on the colonic epithelial proliferation rate.

PATIENTS AND DESIGN Sixteen GH deficient adults were randomised to low dose GH therapy (1 U (0.5 mg) subcutaneously per day, n = 5), high dose GH therapy (2 U daily, n = 5) or placebo (n = 6) during 6 months. Thereafter, all patients were treated with 2 U of GH daily during a 6-months open extension period.

MEASUREMENTS Plasma Insulin-like growth hormone I (IGF-I) and IGF binding protein 3 (IGF BP3) concentrations were measured using commercial RIA kits. The colonic epithelial proliferation rate, expressed as overall crypt labelling index (LI) using 5-bromo-2'-deoxyuridine (BrdU) immunostaining, was determined at baseline, after 6 months **treatment** and at the end of the 6 months open extension period.

RESULTS IGF-I rose from 8.9 +/- 6.7 to 34.6 +/- 20.0 nmol/l after 6 months in 8 GH treated patients ($P < 0.01$ from baseline; $P < 0.01$ from change with placebo). In the extension study, plasma IGF-I was also increased in the patients who previously received placebo ($P < 0.02$, n = 5). LI was evaluable in 14 biopsies at baseline, in 16 after 6 months and in 14 after 12 months. Overall crypt LI did not change in 8 GH treated patients after 6 months ($P > 0.40$ from baseline; $P > 0.80$ from change with placebo). In the extension study, overall crypt LI was also unchanged in those patients who received GH after placebo (n = 5, $P > 0.40$) and in those who continued GH replacement (n = 9, $P > 0.60$; $P > 0.80$ from change

the risk of development of colorectal cancer.

L35 ANSWER 10 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:12464 The Genuine Article (R) Number: 267ZF. Myelin basic protein (MBP) and MBP peptides are mitogens for cultured astrocytes. South S A; Deibler G E; Tzeng S F; Badache A; Kirchner M G; Muja N; **DeVries G H (Reprint)**. EDWARD HINES JR VET ADM HOSP, RES SERV 151, 5TH AVE & ROOSEVELT RD, RM C423, HINES, IL 60141 (Reprint); EDWARD HINES JR VET ADM HOSP, RES SERV 151, HINES, IL 60141; LOYOLA UNIV, STRITCH SCH MED, DEPT CELL BIOL NEUROBIOL & ANAT, MAYWOOD, IL; LOYOLA UNIV, STRITCH SCH MED, PROGRAM NEUROSCI, MAYWOOD, IL; NIMH, CEREBRAL METAB LAB, NIH, BETHESDA, MD; VIRGINIA COMMONWEALTH UNIV, MED COLL VIRGINIA, DEPT BIOCHEM & MOL BIOPHYS, RICHMOND, VA 23298. GLIA (1 JAN 2000) Vol. 29, No. 1, pp. 81-90. Publisher: WILEY-LISS. DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012. ISSN: 0894-1491. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB After CNS demyelination, astrogliosis interferes with axonal regeneration and remyelination. We now provide evidence that myelin basic protein (MBP) can contribute to this observed astrocyte proliferation. We found that astrocytes grown in either serum-containing or serum-free medium proliferate in response to MBP. The mitogenic regions of MBP in both media were MBP1-44, MBP88-151 and MBP152-167. The mitogenic effect of these individual peptides was potentiated by simultaneous **treatment** with microglia conditioned media (CM). MBP-induced proliferation was inhibited by suramin at concentrations known to block the fibroblast growth factor receptor (FGFR), whereas neither MBP1-44, MBP88-151 nor MBP152-167 were affected. Cholera toxin B, that binds to ganglioside GM(1), inhibited the mitogenicity of MBP1-44 and had no significant effect on the mitogenicity of MBP, MBP88-151 or MBP152-167. **Treatment** of astrocytes with MBP and MBP152-167 caused a modest and transitory elevation of intracellular calcium, whereas **treatment** with MBP1-44 resulted in a substantial and sustained increase in intracellular calcium. These results suggest that for cultured astrocytes 1) FGFR and extracellular calcium play a major role in MBP mitogenicity; 2) MBP1-44, MBP88-151 and MBP152-167 are the mitogenic regions of MBP; 3) MBP1-44 and MBP152-167 interact with ganglioside GM(1) and FGFR, respectively; 4) Component(s) present in microglial CM potentiate the mitogenicity of MBP1-44, MBP88-151 and MBP152-167. These data support the hypothesis that MBP related peptides in conjunction with microglial secreted factors may stimulate astrogliosis after demyelination in vivo. GLIA 29:81-90, 2000. (C) 2000 Wiley-Liss, Inc.

L35 ANSWER 11 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:692823 The Genuine Article (R) Number: 351UK. Influence of gonadal hormones on the development of parental behavior in adult virgin prairie voles (Microtus ochrogaster). Lonstein J S (Reprint); **DeVries G J** . UNIV MASSACHUSETTS, CTR NEUROENDOCRINE STUDIES, TOBIN HALL, BOX 37720, AMHERST, MA 01003 (Reprint). BEHAVIOURAL BRAIN RESEARCH (SEP 2000) Vol. 114, No. 1-2, pp. 79-87. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0166-4328. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Prairie voles (Microtus ochrogaster) are a socially monogamous species and both sexes are parental after the birth of pups. In contrast, sexually inexperienced adult prairie voles differ in their behavior towards pups such that virgin males are paternal whereas virgin females are often infanticidal. To test whether there exists a discrete perinatal 'sensitive

gestational period or postnatally on days 1-7. None of the **treatments** altered the high paternal responsiveness of males or the high infanticide rate in females when compared with controls. Females exposed prenatally to ATD, however, had levels of parental behavior that were significantly higher than the lowest levels observed in prenatally TP-treated females. These results suggest that sex differences in the parental behavior of adult virgin prairie voles are not generated exclusively by androgenic or estrogenic mechanisms during a restricted prenatal or early postnatal 'sensitive period' and that the parental behavior of virgin females may be more susceptible to any influence of gonadal hormones during development than males. (C) 2000 Elsevier Science B.V. All rights reserved.

L35 ANSWER 12 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:92426 Document No.: PREV200100092426. Glial changes following sensorimotor cortical lesion and blockade of the neurite inhibitory protein Nogo-A in adult rats. Tsai, S. Y. [Reprint author]; **DeVries, G. H.**; Schwab, M. E.; Kartje, G. L.. Hines VA Hospital, Hines, IL, USA. Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-505.3. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295. Language: English.

AB Our previous work has shown that blockade of the neurite inhibitory protein Nogo-A following adult sensorimotor cortical aspiration lesions resulted in corticofugal plasticity and new neuroanatomical connections from the opposite, unablated cortex (J. Comp. Neurol. 410:143-157, 1999; Ann. Neurol. 45:778-786, 1999). The present study was undertaken to investigate whether blockade of Nogo-A affected glial response after cortical lesions. Adult Long-Evans, black-hooded rats underwent cortical aspiration lesions and were treated with IN-1 antibody (Ab) to block Nogo-A, control Ab, or no Ab. After 8 days survival, animals were perfused, brains were sectioned and examined for astrocytic (GFAP) and microglial (tomato lectin) responses. Our preliminary results showed an increased astrocytic response on the lesioned side compared to the opposite hemisphere with no obvious difference between **treatment** groups. However, an enhancement of the microglial response was observed in subcortical regions of the IN-1 Ab treated animals. These results suggest that microglial changes may be involved in the cellular mechanisms underlying neuroplasticity following Nogo-A blockade. Further studies are undergoing to examine various glial markers and specific growth factors which may be important in regulation of neuroplasticity.

L35 ANSWER 13 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:87771 Document No.: PREV200100087771. Neuregulin and erb-B receptor expression following focal ischemic brain injury in adult rats. Deadwyler, G. D. [Reprint author]; Kartje, G. L.; **DeVries, G. H.**. Hines VA Hospital, Hines, IL, USA. Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-281.6. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295. Language: English.

AB Stroke is a major clinical problem with virtually no **treatment** available to restore neuronal activity after ischemic death. Neuregulins (NRGs), a diverse family of growth factors which bind to the erbB family of tyrosine kinase receptors, have been shown to be beneficial in animal models of neural injury and peripheral neuropathy (Annals New York Acad.

(MCAO). Immunoblotting revealed low levels of HRGalpha and HRGbeta expression in the cerebral cortices and cerebelli of the normal rat brain. Twenty-four hours after MCAO, HRGalpha and HRGbeta immunoreactivity was not detected in the area of infarct (left sensorimotor cortex). In contrast, there was a dramatic increase in HRGalpha expression in the cortical areas immediately around the lesion (left frontal, temporal and occipital cortex) and distal sites (left and right cerebellum). No significant increase in HRGbeta expression was detected in these same brain regions. ErbB3 receptor immunoreactivity was only detected in the opposite sensorimotor cortex 24 hours after MCAO. The increase in HRGalpha expression and the detection of erbB receptor immunoreactivity suggests a possible role for NRGs in cell survival following focal ischemic brain injury.

L35 ANSWER 14 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:134512 Document No.: PREV200100134512. Effects of amphetamine and environmental stimulation on growth associated protein expression following brain injury in the adult rat. Ramic, M. [Reprint author]; Yess, J.; **DeVries, G. H.**; Kartie, G. L.. Loyola University, Maywood, IL, USA. Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-794.14. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295. Language: English.

AB Previous clinical and experimental studies have indicated that a combination of amphetamine and rehabilitation as **treatment** following brain injury results in functional recovery. Growth associated protein (GAP-43) is a known plasticity marker with an essential role in neuronal growth cone extension and guidance during development, regeneration and plasticity. The phosphorylated form (P-GAP-43) is the active state of the protein. We hypothesize that amphetamine **treatment** combined with rehabilitation (social and environmental stimulation - SES) will result in recovery of function due to enhanced neuronal plasticity as measured by P-GAP-43. Adult rats underwent left sensorimotor cortex aspiration lesion and were treated either with amphetamine (given at 2 mg/kg i.p. 48 hours and 120 hours following injury) or both amphetamine and SES. The control group received a cortical lesion only. After a 7 day survival period animals were sacrificed and brains examined for both total GAP-43 and P-GAP-43 by Western blotting and imunocytochemistry. Total GAP-43 was detected in the cortex surrounding the lesion and in the contralateral, opposite sensorimotor cortex in all animals. In contrast, active/P-GAP-43 was only detected in these regions in the animals treated with amphetamine and SES. We conclude that the combination of amphetamine and SES results in GAP-43 phosphorylation/activation which may lead to neuroanatomical plasticity and thereby recovery of function after brain injury.

L35 ANSWER 15 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:492649 The Genuine Article (R) Number: 208JL. Androstenedione effects on the vasopressin innervation of the rat brain. Villalba C; Auger C J; **DeVries G J (Reprint)**. UNIV MASSACHUSETTS, CTR NEUROENDOCRINE STUDIES, NEUROSCI & BEHAV PROGRAM & DEPT PSYCHOL, AMHERST, MA 01003 (Reprint); UNIV MASSACHUSETTS, CTR NEUROENDOCRINE STUDIES, NEUROSCI & BEHAV PROGRAM & DEPT PSYCHOL, AMHERST, MA 01003. ENDOCRINOLOGY (JUL 1999) Vol. 140, No. 7, pp. 3383-3386. Publisher: ENDOCRINE SOC. 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110. ISSN: 0013-7227. Pub. country: USA. Language: English.

the stria terminalis and the centromedial amygdala, and their projections. Adult male rats were castrated and mimic the effects of testosterone on testosterone-responsive neural systems. given testosterone, androstenedione or no hormonal **treatment** for five weeks. Their brains were then processed for vasopressin immunoreactivity. Androstenedione and testosterone **treatment** were equally effective in preventing the reduction of vasopressin immunoreactivity associated with castration. Androstenedione may therefore be able to mimic the effects of testosterone on testosterone-responsive neural system.

L35 ANSWER 16 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:416290 The Genuine Article (R) Number: 199GA. Measurement of agonist and antagonist ligand-binding parameters at the human parathyroid hormone type 1 receptor: Evaluation of receptor states and modulation by guanine nucleotide. Hoare S R J; **DeVries G**; Usdin T B (Reprint). ROOM 3D06, BLDG 36, 36 CONVENT DR, BETHESDA, MD 20892 (Reprint); NIMH, CELL BIOL UNIT, GENET LAB, NIH, BETHESDA, MD 20892; NIDDKD, MATH RES BRANCH, NIH, BETHESDA, MD 20892. JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS (JUN 1999) Vol. 289, No. 3, pp. 1323-1333. Publisher: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0022-3565. Pub. country: USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Determination of ligand-binding constants for parathyroid hormone (PTH) receptors has been hampered by a lack of suitable experimental systems and mechanistic models for data analysis. In this study, ligand binding to the cloned human PTH-1 receptor was measured using membrane-based radioligand-binding assays. Guanosine 5'-O-(3-thiotriphosphate) (GTP gamma S) (10 mu M) reduced binding of agonist radioligands [I-125]rPTH(1-34) and [I-125]PTHrP(1-36) but only to a limited extent (by 29 +/- 5 and 42 +/- 3%, respectively). Radiolabeled agonist dissociation was described by three and two phases in the absence and presence of GTP gamma S, respectively. GTP gamma S **treatment** removed a pseudoirreversible binding phase. Inhibition of radiolabeled antagonist ([I-125]bPTH(3-34)) binding was measured using a 90-min incubation, which allowed binding of ligands to closely approach the asymptotic maximum. Agonist/[I-125]bPTH(3-34) displacement curves were fitted best by assuming two independent affinity states, both in the presence and absence of GTP gamma S. After a 3-h incubation, binding of PTH agonists in the presence of GTP gamma S was described by a single affinity state, indicating the presence of slow components in the binding reaction. Antagonist binding was described by a single affinity state and was not significantly affected by GTP gamma S. The data were used to evaluate potential receptor-binding models. Although other models could not be excluded, all of the observations could be explained by assuming two binding sites on the receptor that recognize two corresponding sites on agonist ligands, Using the model, it was possible to estimate receptor-ligand-binding constants and to propose a direct method for identifying ligands that interact with a putative antagonist binding region of the receptor.

L35 ANSWER 17 OF 50 MEDLINE on STN DUPLICATE 3
1999235517. PubMed ID: 10220111. Phosphorylation of CREB in axon-induced Schwann cell proliferation. Lee M M; Badache A; **DeVries G H.** (Mental Retardation Research Center, Department of Neurobiology, University of California School of Medicine, Los Angeles, USA.) Journal of neuroscience research, (1999 Mar 15) 55 (6) 702-12. Journal code: 7600111. ISSN: 0360-4012. Pub. country: United States. Language: English.

AB Axonal contact regulates Schwann cell (SC) proliferation during

pathway(s) which regulate the phosphorylation of CREB that correlate with the SC proliferative response. The phosphorylated form of CREB was significantly increased after 16 hr of axonal stimulation, continued to increase for 48 hr, and subsequently decreased as monitored by immunocytochemistry and Western blot analysis. **Treatment** with protein kinase A (PKA) inhibitor, H89, completely abolished both the CREB activation and SC proliferation. In contrast, **treatment** with protein kinase C (PKC) inhibitor (bisindolylmaleimide) inhibited AEF-induced SC proliferation, but did not immediately affect CREB phosphorylation. These data are consistent with the view that PKA and PKC pathways are essential for AEF-induced SC proliferation. Since PKC can influence SC proliferation without initially affecting CREB phosphorylation, PKC may regulate SC proliferation at pathways distal to the immediate CREB activation.

L35 ANSWER 18 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:626720 The Genuine Article (R) Number: 224QJ. Improvement and renewal of healthcare processes: results of an empirical research project. vanderBij J D (Reprint); Dijkstra L; **deVries G**; Walburg J. EINDHOVEN UNIV TECHNOL, FAC TECHNOL MANAGEMENT, POB 513, NL-5600 MB EINDHOVEN, NETHERLANDS (Reprint). HEALTH POLICY (AUG 1999) Vol. 48, No. 2, pp. 135-152. Publisher: ELSEVIER SCI IRELAND LTD. CUSTOMER RELATIONS MANAGER, BAY 15, SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND. ISSN: 0168-8510. Pub. country: NETHERLANDS. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Professionals in healthcare organizations, who generally produce high-quality work, commonly operate in isolation or locally. However, due to developments in society and legislation, healthcare organizations are forced to integrate healthcare activities, and achieve integral quality management, instead of suboptimal, local quality management. Eindhoven University of Technology set up a study in 11 Dutch healthcare organizations in the area of interface management. The study was performed in general and mental hospitals, and clinics for care and **treatment** of drug addicts. The research projects aimed to develop methods to achieve an improvement or a renewal of healthcare processes. Special attention was paid to the interfaces between departments and individual parts of the healthcare process. In this paper an outline is given of both the improvement and the renewal approach, results of three of the 11 case studies are presented (as an example) and the improvement and the renewal approach are compared with respect to healthcare processes.

L35 ANSWER 19 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
97:447704 The Genuine Article (R) Number: XC745. Detection of circulating prostate carcinoma cells via an enhanced reverse transcriptase-polymerase chain reaction assay in patients with early stage prostate carcinoma - Independence from other pretreatment characteristics. Ennis R D (Reprint); Katz A E; **deVries G M**; Heitjan D F; OToole K M; Rubin M; Buttyan R; Benson M C; Schiff P B. COLUMBIA UNIV, COLL PHYS & SURG, DEPT RADIAT ONCOL, 622 W 168TH ST, NEW YORK, NY 10032 (Reprint); COLUMBIA UNIV COLL PHYS & SURG, DEPT UROL, NEW YORK, NY 10032; COLUMBIA UNIV, SCH PUBL HLTH, DIV BIOSTAT, NEW YORK, NY 10032; COLUMBIA UNIV, COLL PHYS & SURG, DEPT PATHOL, NEW YORK, NY. CANCER (15 JUN 1997) Vol. 79, No. 12, pp. 2402-2408. Publisher: WILEY-LISS. DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012. ISSN: 0008-543X. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

METHODS. Two hundred and twenty-seven patients with clinically localized adenocarcinoma of the prostate had an RT-PCR assay performed as part of their staging evaluation. No **treatment** decisions were made on the basis of the RT-PCR results. Of these, 156 patients were treated with radical prostatectomy (RP) and 71 with radical external beam radiotherapy (EBRT). Forty-eight patients were treated with hormonal therapy prior to RP (n = 39) or EBRT (n = 9). The prognostic factors analyzed for their relationship to RT-PCR were clinical stage, pretreatment serum PSA levels, Gleason score of the biopsy specimen, and Gleason score of the surgical specimen. An analysis of the relationship between **treatment** and RT-PCR results was also performed. Multivariate logistic regression analysis of predictors of RT-PCR positivity was performed as well. In addition, univariate and multivariate analyses of predictors of pathologic stage, including RT-PCR, were performed.

RESULTS. Sixty-one patients (26.9%) had a positive RT-PCR assay. There was no relationship between clinical stage, pretreatment PSA, biopsy Gleason score, or surgical Gleason score and RT-PCR positivity. In univariate analysis, patients treated with RP had a higher rate of RT-PCR positivity than patients treated with EBRT ($P = 0.054$). However, in multivariate logistic regression analysis no factor, including **treatment** with RP, was a significant predictor of RT-PCR positivity. RT-PCR and pretreatment PSA predicted pathologic stage in univariate and multivariate analyses ($P < 0.0001$ and $P = 0.002$, respectively).

CONCLUSIONS. The detection of circulating prostate cells using RT-PCR occurs in approximately 25% of early stage prostate carcinoma patients and is independent of other established prognostic factors. In addition, a positive RT-PCR assay is a strong predictor of pathologic upstaging in patients with clinically organ-confined disease. (C) 1997 American Cancer Society.

L35 ANSWER 20 OF 50 MEDLINE on STN DUPLICATE 4

97475097. PubMed ID: 9334621. Pretreatment prostate specific antigen doubling times: use in patients before radical prostatectomy. Goluboff E T; Heitjan D F; **DeVries G M**; Katz A E; Benson M C; Olsson C A. (Department of Urology, College of Physicians and Surgeons, Columbia University, New York, New York, USA.) Journal of urology, (1997 Nov) 158 (5) 1876-8; discussion 1878-9. Journal code: 0376374. ISSN: 0022-5347. Pub. country: United States. Language: English.

AB PURPOSE: We determined whether pre-radical prostatectomy prostate specific antigen (PSA) doubling time could predict pathological stage at radical prostatectomy or PSA failure postoperatively. We also sought to compare PSA doubling times from men with prostate cancer treated with radical prostatectomy to a group treated with radiation therapy. MATERIALS AND METHODS: Detailed followup was available for 150 patients with clinically localized prostate cancer who underwent radical prostatectomy from January 1993 to August 1995. PSA doubling time was calculated for all patients with 3 or more pre-radical prostatectomy PSA levels using linear regression. We assessed the association between PSA doubling time and PSA failure, pathologic stage at radical prostatectomy, final PSA before **treatment** and Gleason score. We compared our PSA doubling time values and distribution to a published series of patients with prostate cancer who had undergone radiation therapy. RESULTS: A total of 56 patients had 3 or more PSA values before **treatment**. Median followup was 17.3 months. PSA doubling time did not correlate with PSA failure, final PSA or Gleason score, but it did with pathological stage at

finding. We did find a correlation with pathologic stage at radical prostatectomy, and so longer followup with more patients may confirm this in the future. We also found no significant differences in PSA doubling time between our patients and a group treated with radiation. At least for this parameter, patients with prostate cancer referred for radical prostatectomy and radiation therapy may be similar.

L35 ANSWER 21 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
97:240689 The Genuine Article (R) Number: WN186. Effect of systemic corticosteroid **treatment** on choroidal neovascularization in the rat.. **DeVries G W (Reprint)**; Bullington R; Edelman J L. ALLERGAN PHARMACEUT INC, DEPT SCI BIOL, IRVINE, CA 92715. INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (15 MAR 1997) Vol. 38, No. 4, Part 1, pp. 1332-1332. Publisher: LIPPINCOTT-RAVEN PUBL. 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106. ISSN: 0146-0404. Pub. country: USA. Language: English.

L35 ANSWER 22 OF 50 MEDLINE on STN DUPLICATE 5
1998078772. PubMed ID: 9418963. Effect of neu differentiation factor isoforms on neonatal oligodendrocyte function. Raabe T D; Suy S; Welcher A; **DeVries G H.** (Department of Cell Biology, Neurobiology, and Anatomy, Loyola University Medical Center, Maywood, Illinois, USA.) Journal of neuroscience research, (1997 Dec 1) 50 (5) 755-68. Journal code: 7600111. ISSN: 0360-4012. Pub. country: United States. Language: English.

AB Previous studies have suggested that neu differentiation factor (NDF), a member of the neuregulin (NRG) family of growth factors, may regulate the development of PNS and CNS glial cells. There is limited information concerning the potential role of NDF on the development of neonatal (immature) oligodendrocytes (OLG) into adult OLG. We now report the effect of the two major isoform families of NDF (NDF alpha and NDF beta) on the development of cultured rat neonatal OLG. Immunocytochemical and western blot analyses of neonatal OLG using anti-erb-B antibodies revealed that these immature OLG express all four members of NRG (erb-B) receptors. **Treatment** of neonatal OLG with varying concentrations of either NDF alpha or NDF beta did not have a mitogenic effect on cultured neonatal OLG. Pretreatment of immature OLG with either of the NDF isoforms also did not influence the subsequent mitogenicity of other known OLG mitogens. However, **treatment** of neonatal OLG with either isoform of NDF influenced the survival of these cells by protecting the cells from apoptosis. Additionally, **treatment** of neonatal OLG with either NDF alpha or NDF beta resulted in more extensive process formation compared to control, non-treated OLG.

L35 ANSWER 23 OF 50 MEDLINE on STN DUPLICATE 6
97244369. PubMed ID: 9089209. Immunolocalization of cytoplasmic and myelin mcalpain in transfected Schwann cells: II. Effect of withdrawal of growth factors. Chakrabarti A K; Neuberger T; Russell T; Banik N L; **DeVries G H.** (Department of Neurology, Medical University of South Carolina, Charleston 29425, USA.) Journal of neuroscience research, (1997 Mar 15) 47 (6) 609-16. Journal code: 7600111. ISSN: 0360-4012. Pub. country: United States. Language: English.

AB We have examined the reversal of the regulatory effect of growth factors on calpain/calpastatin activity in transfected Schwann cells (tSc) after their subsequent withdrawal. Removal of nerve growth factor (NGF) or cyclic adenosine monophosphate (cAMP) from tSc resulted in a smaller loss of mu calpain (37%) and mcalpain (36.5 %) activity compared to treated

following withdrawal of various growth factors, including NGF, cAMP, aFGF, bFGF, platelet-derived growth factor aa (PDGFaa), and PDGFbb. The inhibitory activity of calpastatin was greater than control following withdrawal of NGF, cAMP, PDGFaa, or PDGFbb at 24 hr and this inhibitory activity was less with **treatment** by aFGF and bFGF. The control activity was restored at 48 hr following withdrawal of these factors. The intensity of the cytoplasmic calpain immunoreactivity was significantly decreased in the nuclear and non-nuclear regions of the cytoplasm, respectively, following withdrawal of cAMP at 144 hr. Removal of bFGF from the medium resulted in an increase of cytoplasmic calpain immunoreactivity in the nuclear regions and cytoplasm, while there was dramatic loss of myelin calpain immunoreactivity from both the nuclear region and cytoplasm. The changes in calpain activity and immunoreactivity in tSc following withdrawal of growth factors suggest that release of calpain from membrane to cytosol may be regulated by these factors.

L35 ANSWER 24 OF 50 MEDLINE on STN DUPLICATE 7

97220699. PubMed ID: 9067861. Immunolocalization of cytoplasmic and myelin mcalpain in transfected Schwann cells: I. Effect of **treatment** with growth factors. Neuberger T; Chakrabarti A K; Russell T; **DeVries G H**; Hogan E L; Banik N L. (Department of Neurology, Medical University of South Carolina, Charleston.) Journal of neuroscience research, (1997 Mar 1) 47 (5) 521-30. Journal code: 7600111. ISSN: 0360-4012. Pub. country: United States. Language: English.

AB We have examined the effect of growth factors on the activity and localization of calpain in transfected Schwann cells (tSc). Axolemma-enriched fraction, cAMP, or NGF showed concentration-dependent inhibition of both mu calpain and mcalpain activity. In contrast, both acidic FGF and basic FGF stimulated mu calpain (37%) and mcalpain (58%) of tSC while PDGF-aa and PDGF-bb inhibited both calpain activities. The inhibitor (calpastatin) activity was approximately 90% following **treatment** with NGF, cAMP, PDGF-aa, and PDGF-bb compared to control while this activity was 40% with FGF-treated samples. Immunofluorescence studies indicated localization of cytoplasmic calpain in the nuclear region following growth factor **treatment** in the cytoplasm. Growth factor **treatment** caused a decrease in the intensity of calpain immunoreactivity. **Treatment** with cAMP or FGF resulted in strong immunoreactivity of mcalpain in the nuclear region and cytoplasm compared to untreated. The growth factors did not cause translocation of calpain to the outer surface of the cell membrane. The increased immunoreactivity seen with myelin calpain antibody was greater than cytosolic antibody. The changes seen in calpain activity and immunoreactivity following **treatment** with growth factors suggest that these factors may regulate calpain-calpastatin expression and translocation to the membrane for interaction with lipids for enzyme activation.

L35 ANSWER 25 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

1997:286344 Document No.: PREV199799585547. Effect of systemic corticosteroid **treatment** on choroidal neovascularization in the rat.
Devries, G. W.; Bullington, R.; Edelman, J. L.. Dep. Biol. Sci., Allergan, Irvine, CA, USA. Investigative Ophthalmology and Visual Science, (1997) Vol. 38, No. 4 PART 1-2, pp. S286.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology, Parts 1-2. Fort Lauderdale, Florida, USA. May 11-16, 1997.

Caliguri E J; **DeVries G J (Reprint)**. UNIV MASSACHUSETTS, DEPT PSYCHOL, NEUROSCI & BEHAV PROGRAM, TOBIN HALL, AMHERST, MA 01003 (Reprint); UNIV MASSACHUSETTS, DEPT PSYCHOL, NEUROSCI & BEHAV PROGRAM, AMHERST, MA 01003; WELLESLEY COLL, DEPT CHEM, WELLESLEY, MA 02181. HORMONES AND BEHAVIOR (DEC 1997) Vol. 32, No. 3, pp. 184-191. Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0018-506X. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The selective serotonin reuptake inhibitor fluoxetine modifies social behavior in a number of species, including humans. Because the neural substrates for social behavior in prairie voles are sexually dimorphic, we tested whether the effects of fluoxetine on these behaviors differ by sex. Parental and pair-bonded voles were chronically treated with fluoxetine or saline and subsequently tested for parental responsiveness. Fluoxetine-treated animals displayed a longer latency to exhibit parental responsiveness than did saline-treated controls ($p < 0.02$), but they did not differ in other aspects of parental care. There were no sex differences in the effects of fluoxetine on parental behavior. After completion of the tests for parental behavior, the subjects were tested for aggressive behavior using the resident-intruder paradigm. Fluoxetine-treated males displayed less aggressive behavior than their saline-treated counterparts , < 0.02). Although we did not find any effects of fluoxetine on aggressive behavior in females, no significant interaction was found between sex and **treatment**. Fluoxetine did not alter nonsocial behaviors. The findings suggest that serotonin influences social behavior in prairie voles. (C) 1997 Academic Press.

L35 ANSWER 27 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1998:126419 The Genuine Article (R) Number: YV282. Masculine sexual behavior is disrupted in male and female mice lacking a functional estrogen receptor alpha gene. Wersinger S R (Reprint); Sannen K; Villalba C; Lubahn D B; Rissman E F; **DeVries G J**. UNIV VIRGINIA, DEPT BIOL, GILMER HALL, CHARLOTTESVILLE, VA 22903 (Reprint); UNIV MASSACHUSETTS, DEPT PSYCHOL, NEUROSCI & BEHAV PROGRAM, AMHERST, MA 01003; UNIV MISSOURI, DEPT BIOCHEM, COLUMBIA, MO 65211; UNIV MISSOURI, DEPT CHILD HLTH, COLUMBIA, MO 65211. HORMONES AND BEHAVIOR (DEC 1997) Vol. 32, No. 3, pp. 176-183. Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0018-506X. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Masculine sexual behavior is regulated by testosterone (T). However, T can be metabolized to form estrogens or other androgens, which then activate their own receptors. We used knockout mice lacking a functional estrogen receptor alpha(ER alpha) gene to test the hypothesis that, following aromatization, T acts via the ER alpha to activate normal masculine sexual behavior. After gonadectomy and T replacement, wild-type (WT) male and female mice displayed masculine behavior. However, given the same T **treatment**, little masculine behavior was displayed by mice of either sex that lack a normal copy of the ER alpha gene. In particular, the latency to display masculine sex behavior and the number of mount attempts per trial were significantly reduced in the ER alpha(-) mice compared to WT littermates ($P < 0.05$). In addition, we found that in both sexes, EU alpha(-) mice have a smaller cluster of androgen receptor immunoreactivity in the bed nucleus of the stria terminalis. Using adult ER alpha(-) mice we were unable to determine whether these genotypic differences are due to organizational or activational effects. However, it is clear that the ER alpha plays a key role in the expression of masculine

REVERSE-TRANSCRIPTASE POLYMERASE CHAIN-REACTION FOR PROSTATE-SPECIFIC ANTIGEN PREDICTS **TREATMENT** FAILURE FOLLOWING RADICAL PROSTATECTOMY. OLSSON C A (Reprint); **DEVRIES G M**; RAFFO A J; BENSON M C; OTOOLE K; CAO Y C; BUTTYAN R E; KATZ A E. COLUMBIA UNIV COLL PHYS & SURG, DEPT UROL, NEW YORK, NY, 10032 (Reprint); COLUMBIA UNIV COLL PHYS & SURG, DEPT PATHOL, NEW YORK, NY, 10032. JOURNAL OF UROLOGY (MAY 1996) Vol. 155, No. 5, pp. 1557-1562. ISSN: 0022-5347. Pub. country: USA. Language: ENGLISH.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose: We previously demonstrated than an enhanced reverse transcriptase-polymerase chain reaction assay for prostate specific antigen (PSA) can predict final pathological stage in radical prostatectomy patients. The potential role of the assay in predicting serum PSA recurrence after radical prostatectomy was explored.

Materials and Methods: We evaluated 100 radical prostatectomy candidates by reverse transcriptase polymerase chain reaction preoperatively, and status was compared to serum PSA, Gleason score and final pathological results, Potential surgical failure was defined as tumor at the surgical margin or extending into the seminal vesicle. Patients were monitored postoperatively by serum PSA every 4 months. Kaplan-Meier analysis was used to evaluate the correlation between reverse transcriptase polymerase chain reaction and disease recurrence, defined as a PSA of 0.2 ng./ml. or greater.

Results: Enhanced reverse transcriptase polymerase chain reaction for PSA had a stronger correlation with potential surgical failure than preoperative serum PSA or Gleason score (relative risks 15.2, 5.9 and 3.2, respectively). The correlation between these modalities and PSA recurrence was evaluated during a mean followup of 13.6 months (range 5 to 26). Of 36 patients with positive reverse transcriptase polymerase chain reactions 9 had failure by PSA compared to 3 of 64 (4.7%) with negative polymerase chain reactions ($p < 0.0286$). The relative risk for failure by reverse transcriptase polymerase chain reaction was 3.6. Gleason score and serum PSA had higher correlations with postoperative PSA elevations (relative risk 13.2 and 7.6, respectively). A Cox regression analysis model demonstrated that reverse transcriptase polymerase chain reaction for PSA can be used in conjunction with Gleason score and provides statistically significant risk information.

Conclusions: Enhanced reverse transcriptase polymerase chain reaction for PSA is a statistically significant predictor of potential failure by pathological analysis and of disease recurrence by PSA. Longer followup data are required to define further the role of the assay in the management of patients with prostate cancer.

L35 ANSWER 29 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

96:807416 The Genuine Article (R) Number: VQ500. SCHWANN-CELLS STIMULATED BY AXOLEMMA-ENRICHED FRACTIONS EXPRESS CYCLIC-AMP RESPONSIVE ELEMENT-BINDING PROTEIN. LEE M M S; SATOBIGBEE C; **DEVRIES G H (Reprint)**. EDWARD HINES JR VET ADM HOSP, RES 151, HINES, IL, 60141 (Reprint); EDWARD HINES JR VET ADM HOSP, HINES, IL, 60141; LOYOLA UNIV, MED CTR, DEPT CELL BIOL NEUROBIOL & ANAT, MAYWOOD, IL, 60153; VIRGINIA COMMONWEALTH UNIV, MED COLL VIRGINIA, DEPT BIOCHEM & MOL BIOPHYS, RICHMOND, VA, 23298. JOURNAL OF NEUROSCIENCE RESEARCH (15 OCT 1996) Vol. 46, No. 2, pp. 204-210. ISSN: 0360-4012. Pub. country: USA. Language: ENGLISH.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Both axolemma-enriched fractions (AEF) and cyclic AMP have been shown to regulate the proliferation and differentiation of cultured primary Schwann cells (SC), We have evaluated the role of CREB, a transcription

antibodies and western blot analysis, after 24 hr of AEF **treatment** we first detected CREB as a 45 kDa protein which reached a maximal level of expression after 72 hr, Double labelled immunocytochemistry using anti-CREB and anti-5-bromo-2'-deoxy-uridine antibodies demonstrated maximal CREB expression after 72 hr of AEF **treatment**, closely coinciding with the temporal expression of SC proliferation, At all times examined, all AEF-treated SC labelled by anti-CREB antibodies were also labelled with anti-BrdU antibodies, These observations are consistent with the view that CREB could play an important role in the induction of SC proliferation by AEF. (C) 1996 Wiley-Liss, Inc.

L35 ANSWER 30 OF 50 MEDLINE on STN DUPLICATE 8

97047190. PubMed ID: 8892110. **Treatment** of oligodendrocytes with antisense deoxyoligonucleotide directed against CREB mRNA: effect on the cyclic AMP-dependent induction of myelin basic protein expression. Sato-Bigbee C; **DeVries G H.** (Department of Biochemistry and Molecular Biophysics, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298-0614, USA.) Journal of neuroscience research, (1996 Oct 1) 46 (1) 98-107. Journal code: 7600111. ISSN: 0360-4012. Pub. country: United States. Language: English.

AB We have shown previously that in oligodendrocytes, the transcription factor cyclic AMP response element binding protein (CREB) is maximally expressed immediately prior to the most rapid period of myelination in rat brain. We have begun to investigate the role of this protein during myelination by downregulating CREB synthesis in cultured oligodendrocytes using an antisense deoxyoligonucleotide directed against CREB mRNA. Neonatal oligodendrocytes were grown for 4 days in a chemically defined medium (CDM) after which intracellular delivery of CREB antisense oligonucleotide was facilitated by using a liposome preparation. Control cultures were treated in a similar manner but in the presence of CREB sense oligomer. Immediately after transfection, cells were cultured for 3 days in CDM in the presence or absence of the cyclic AMP (cAMP) analogue N6, O21-dibutyryl cAMP (db-cAMP). In these cultures, myelin basic protein (MBP) expression was investigated by immunocytochemistry and Western blot analysis. **Treatment** of control cultures with db-cAMP resulted in a significant increase in the number of MBP positive cells which was abolished when the cells were treated with CREB antisense oligonucleotide. MBP positive cells in control cultures treated with db-cAMP have extended and highly branched MBP positive processes. In contrast, MBP positive cells in either control cultures grown in the absence of db-cAMP or cultures grown in the presence of db-cAMP but treated with CREB antisense oligonucleotide showed shorter and less complex processes and the MBP immunoreactivity appeared to be concentrated in the cell body. These observations suggest that CREB is at least one of the mediators in the induction of oligodendrocyte differentiation by cAMP.

L35 ANSWER 31 OF 50 MEDLINE on STN DUPLICATE 9

96331488. PubMed ID: 8760205. Effects of photoperiod and androgen on pituitary function and neuropeptide staining in Siberian hamsters. Bittman E L; Jetton A E; Villalba C; **Devries G J.** (Department of Biology, University of Massachusetts, Amherst 01003, USA.) American journal of physiology, (1996 Jul) 271 (1 Pt 2) R64-72. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.

AB Short photoperiods decrease gonadotropin secretion in Siberian hamsters, but it is unknown whether the negative feedback effects of androgens are amplified under such conditions, as is the case in other species. Photoperiod regulates the synthesis and secretion of gonadotropin-

investigated effects of age on photoperiodic influences on brain peptides and serum hormone levels. Serum prolactin concentrations were regulated by photoperiod and by gonadal status in LD hamsters. Effects of T on follicle-stimulating hormone secretion were more pronounced in SD hamsters. Older hamsters were generally less responsive to effects of daylength on pituitary function. Photoperiod and gonadal status regulated the number of AVP-immunoreactive (ir) cells in the bed nucleus of the stria terminalis and the medial amygdala. Androgen **treatment** yielded more AVP-ir neurons in LD than in SD. Photoperiod influenced the number of GnRH-ir cells only in the medial septum of castrated hamsters. Daylength regulated beta-endorphin-ir neurons in intact hamsters, but not in castrates. Only among old hamsters did photoperiod affect the influence of T on beta-endorphin staining in neurons and fibers. Such fiber staining was unaffected by photoperiod in intact and T-treated castrate hamsters, but was reduced in SD castrates. We conclude that daylength modulates the effects of androgen on gonadotropin secretion and influences the effect of T on neuropeptide staining in regionally specific patterns that depend on the age of the animal and its history of prior steroid exposure.

L35 ANSWER 32 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
96:540123 The Genuine Article (R) Number: UW723. EFFECTS OF PHOTOPERIOD AND ANDROGEN ON PITUITARY-FUNCTION AND NEUROPEPTIDE STAINING IN SIBERIAN HAMSTERS. BITTMAN E L (Reprint); JETTON A E; VILLALBA C; **DEVRIES G J**. UNIV MASSACHUSETTS, DEPT BIOL, AMHERST, MA, 01003 (Reprint); UNIV MASSACHUSETTS, DEPT PSYCHOL, AMHERST, MA, 01003; UNIV MASSACHUSETTS, NEUROSCI & BEHAV PROGRAM, AMHERST, MA, 01003. AMERICAN JOURNAL OF PHYSIOLOGY-REGULATORY INTEGRATIVE AND COMPARATIVE PHYSIOLOGY (JUL 1996) Vol. 40, No. 1, pp. R64-R72. ISSN: 0363-6119. Pub. country: USA. Language: ENGLISH.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Short photoperiods decrease gonadotropin secretion in Siberian hamsters, but it is unknown whether the negative feedback. effects of androgens are amplified under such conditions, as is the ease in other species. Photoperiod regulates the synthesis and secretion of gonadotropin-releasing hormone (GnRH), beta-endorphin, and arginine vasopressin (AVP), which influence gonadotropin release and sexual behavior but are themselves regulated by gonadal steroid hormones. To determine the role of androgen in these effects of daylength, immunostaining and gonadotropin concentrations were examined after 8 wk of exposure to long or short days (LD or SD). Animals were either left intact, castrated, or castrated with immediate or delayed replacement of testosterone (T). We also investigated effects of age on photoperiodic influences on brain peptides and serum hormone levels. Serum prolactin concentrations were regulated by photoperiod and by gonadal status in LD hamsters. Effects of T on follicle-stimulating hormone secretion were more pronounced in SD hamsters. Older hamsters were generally less responsive to effects of daylength on pituitary function. Photoperiod and gonadal status regulated the number of AVP-immunoreactive (ir) cells in the bed nucleus of the stria terminalis and the medial amygdala. Androgen **treatment** yielded more AVP-ir neurons in LD than in SD. Photoperiod influenced the number of GnRH-ir cells only in the medial septum of castrated hamsters. Daylength regulated beta-endorphin-ir neurons in intact hamsters, but not in castrates. Only among old hamsters did photoperiod affect the influence of T on beta-endorphin staining in neurons and fibers. Such fiber staining was unaffected by photoperiod in

95:850141 The Genuine Article (R) Number: TJ074. ANDROGEN AND ESTROGEN EFFECTS ON VASOPRESSIN MESSENGER-RNA EXPRESSION IN THE MEDIAL AMYGDALOID NUCLEUS IN MALE AND FEMALE RATS. WANG Z X (Reprint); **DEVRIES G J***. **EMORY UNIV, SCH MED, DEPT PSYCHIAT & BEHAV SCI, 1639 PIERCE DR, ATLANTA, GA, 30322 (Reprint); UNIV MASSACHUSETTS, DEPT PSYCHOL, NEUROSCI & BEHAV PROGRAM, AMHERST, MA, 01003. JOURNAL OF NEUROENDOCRINOLOGY (NOV 1995) Vol. 7, No. 11, pp. 827-831. ISSN: 0953-8194. Pub. country: USA. Language: ENGLISH.**

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Vasopressin messenger RNA (AVP mRNA) expression in the medial amygdala and bed nucleus of the stria terminalis (BST) is almost completely dependent on gonadal steroids. In the BST, the effects of gonadal steroids on AVP mRNA expression are sexually dimorphic. Males have more cells that express AVP mRNA and more AVP mRNA per cell than females. Here we test whether this is also true for the MA.**

In gonadectomized rats that were treated with testosterone, males had more cells that were labeled for AVP mRNA than females. However, the labeling per cell did not differ between males and females. To assess contribution of testosterone metabolites to these differences, male and female rats were gonadectomized and implanted with empty tubing, or tubing filled with dihydrotestosterone (DHT), estradiol (E), or E plus DHT (E + DHT). The pattern of steroid effects on AVP mRNA expression in the MA was similar in both sexes. Hardly any labeled cells were found in rats with empty implants or rats treated with DHT. Significantly more labeled cells were found in rats treated with E, and even more cells in rats treated with Ef DHT. The number of AVP mRNA-labeled cells was higher in males than in females for E as well as E + DHT ***treatment, but the labeling per cell did not differ between sexes. These data suggest that the number of MA cells that can express AVP mRNA is higher in males than in females, but the estrogen and androgen responsiveness of individual AVP mRNA-expressing cells in the MA does not differ between sexes.

L35 ANSWER 34 OF 50 MEDLINE on STN DUPLICATE 10

96263365. PubMed ID: 8847738. Exogenous myelin basic protein promotes oligodendrocyte death via increased calcium influx. Tzeng S F; Deibler G E; **DeVries G H.** (Department of Biochemistry and Molecular Biophysics, Medical College of Virginia, Richmond, USA.) Journal of neuroscience research, (1995 Dec 15) 42 (6) 768-74. Journal code: 7600111. ISSN: 0360-4012. Pub. country: United States. Language: English.

AB **Treatment** of cultured oligodendrocytes (OLGs) with micromolar quantities of myelin basic protein (MBP) caused a rapid, MBP-dose-dependent cell death. In contrast, a 72-hr incubation of OLGs with MBP peptides (1-44, 47-87, 88-151, or 152-167) at comparable concentrations had no effect on cell viability. MBP and MBP peptides (1-44 and 88-151) have been shown to interact with ganglioside GM1 (Tzeng et al.: J Neurochem Res: 42:758-767, 1995). This interaction has been reported to increase calcium influx. Therefore, using the fluorescent dye Indo-1 and an ACAS laser cytometer, we examined the level of intracellular calcium in OLGs after MBP **treatment.** MBP was shown to provoke a rapid, dramatic, and sustained rise of intracellular calcium in most OLGs. The levels of elevated intracellular calcium were sustained and did not return to baseline even after 10 min. This increase of intracellular calcium was suppressed in the presence of EGTA, indicating that the [Ca2+]i rise was due to the entry of extracellular calcium. Incubation of cultured OLGs with MBP peptides (1-44 or 88-151) caused a modest and transitory elevation of intracellular calcium ions in a lower percentage

proliferation in a cAMP dependent process. Tzeng S F; Deibler G E; Neuberger T J; **DeVries G H.** (Department of Biochemistry and Molecular Biophysics, Medical College of Virginia, Richmond, USA.) Journal of neuroscience research, (1995 Dec 15) 42 (6) 758-67. Journal code: 7600111. ISSN: 0360-4012. Pub. country: United States. Language: English.

AB Previous studies have shown that myelin basic protein (MBP) is mitogenic for Schwann cells (SCs) in the presence of elevated intracellular cAMP. Two mitogenic regions of MBP have been identified: one mitogenic region within the first 44 residues of the aminoterminus (1-44) and the other mitogenic region within the terminal 15 residues of the carboxyl end of the molecule (152-167). Unlike the mitogenic effect of a myelin enriched fraction (MEF), the mitogenic effect of MBP was not reduced by the addition of the lysosomal inhibitor, ammonium chloride. These data indicate that MBP causes SC proliferation by direct interaction of MBP with a surface receptor. Using Scatchard analysis of the binding of MBP to SCs, we report that **treatment** with forskolin does not cause the upregulation of receptors for MBP. Moreover, MBP blocks the cross-linking of 125I-bFGF with two fibroblast growth factor (FGF) receptors having apparent molecular weights of 140 kDa and 120 kDa, respectively. Since neither TGF-beta nor PDGF-BB displaced cell surface bound 125I-MBP, we conclude that MBP binds to the FGF receptor rather than other growth factor receptors. Furthermore, only MBP interacted with ganglioside GM1, whereas MBP did not interact with this ganglioside. These results are consistent with the view that ganglioside GM1 mediates the mitogenic effects of MBP, while the FGF receptor mediates the mitogenic effect of MBP. Intracellular cAMP of SCs was transiently increased after the addition of macrophage conditioned medium, suggesting that macrophages may produce factors in vivo which can transiently elevate intracellular cAMP levels, allowing a wave of SC proliferation in response to MBP-related mitogens.

L35 ANSWER 36 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
95:261194 The Genuine Article (R) Number: QQ984. THE ANTIINFLAMMATORY ACTIVITY OF TOPICALLY APPLIED NOVEL CALCIUM-CHANNEL ANTAGONISTS. **DEVRIES G W (Reprint)**; MCLAUGHLIN A; WENZEL M B; PEREZ J; HARCOURT D; LEE G; GARST M; WHEELER L A. ALLERGAN PHARMACEUT INC, DEPT BIOL, IRVINE, CA, 92715 (Reprint); ALLERGAN PHARMACEUT INC, DEPT CHEM SCI, IRVINE, CA, 92715. INFLAMMATION (APR 1995) Vol. 19, No. 2, pp. 261-275. ISSN: 0360-3997. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The antiinflammatory activities of two novel calcium-channel antagonists, AGN 190742 and AGN 190744, were evaluated in murine models of cutaneous inflammation. These 2(5H)-furanone ring compounds block both depolarization-dependent Ca2+ entry and receptor-mediated responses in GH3 cells. Topical application of AGN 190742 or AGN 190744 inhibits neutrophil infiltration and epidermal hyperplasia induced by repeated **treatment** of mouse skin with phorbol ester. AGN 190744 also is active in an arachidonic acid model of acute inflammation. These data suggest that topical application of calcium-channel antagonists can inhibit cutaneous inflammatory responses and that AGN 190742 and/or AGN 190744 may serve as useful pharmacological probes for examining these responses in vivo.

L35 ANSWER 37 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
94:361785 The Genuine Article (R) Number: NP581. DISTRIBUTION OF ANDROGEN

AB Arginine vasopressin-immunoreactive (AVP-ir) neurons in the bed nucleus of stria terminalis (BST) and medial amygdaloid nucleus are very responsive to gonadal hormones. After gonadectomy, these neurons lose their AVP immunoreactivity and stop expressing AVP mRNA. Testosterone **treatment** reverses these changes, acting via androgen as well as estrogen receptor-mediated mechanisms. Although AVP-ir neurons contain estrogen receptor immunoreactivity, it is not known whether they also contain androgen receptor immunoreactivity. To answer this question, brains of male rats were stained immunocytochemically for AVP as well as for androgen receptors. In the BST and medial amygdaloid nucleus, respectively, 90.5% and 91.2% of the AVP-Ir neurons contained androgen receptor immunoreactivity. In contrast, in the suprachiasmatic nucleus, the supraoptic nucleus, and the magnocellular portion of the paraventricular nucleus (PVN), none of the AVP-ir neurons contained androgen receptor immunoreactivity. In the ventral zone of the medial parvocellular part of the PVN (mpvPVN), 4.3% of the scattered AVP-ir neurons contained androgen receptor immunoreactivity. One of the control experiments, ie. staining sections for oxytocin (OT) rather than AVP, revealed that although OT-ir neurons in the supraoptic and magnocellular portion of the PVN did not contain androgen receptor immunoreactivity, 52.5% of the OT-ir neurons in the mpvPVN did. The results suggest that androgens can bind to androgen receptors in AVP-ir neurons in the BST and medial amygdaloid nucleus, possibly to influence AVP expression. The results also suggest that androgens can bind to androgen receptors in AVP-ir and OT-ir neurons in the mpvPVN. The function of the latter interaction, however, is unclear.

L35 ANSWER 38 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
94:171665 The Genuine Article (R) Number: MZ407. SEX-DIFFERENCES IN THE EFFECTS OF TESTOSTERONE AND ITS METABOLITES ON VASOPRESSIN MESSENGER-RNA LEVELS IN THE BED NUCLEUS OF THE STRIA TERMINALIS OF RATS. **DEVRIES G J (Reprint)**; WANG Z X; BULLOCK N A; NUMAN S. UNIV MASSACHUSETTS, DEPT PSYCHOL, AMHERST, MA, 01003 (Reprint); UNIV MASSACHUSETTS, NEUROSCI & BEHAV PROGRAM, AMHERST, MA, 01003. JOURNAL OF NEUROSCIENCE (MAR 1994) Vol. 14, No. 3, Part 2, pp. 1789-1794. ISSN: 0270-6474. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Male rats have about two times as many steroid-responsive vasopressin-immunoreactive (AVP-ir) neurons in the bed nucleus of the stria terminalis (BST) as female rats. This sex difference does not depend on differences in circulating hormone levels, since it persists in males and females that are treated with similar levels of testosterone. To analyze the cellular basis of this sex difference, we compared the effects of testosterone and its metabolites on AVP mRNA expression in the BST of males and females that were gonadectomized at 3 months of age.

When rats received implants of Silastic tubing filled with testosterone, males had more cells that were labeled for AVP mRNA and more labeling per cell than females. When, in a second experiment, rats received implants of either empty tubing, or tubing with dihydrotestosterone (DHT), estradiol(E), or E plus DHT, hardly any labeled cells were found in rats with empty implants. E **treatment** significantly stimulated AVP mRNA expression in both sexes, but significantly more so in males, which had more cells that were labeled for AVP mRNA and more labeling per cell than females. DHT **treatment** by itself did not stimulate AVP mRNA expression, but when given in combination with E, it significantly increased the number of cells over

L35 ANSWER 39 OF 50 MEDLINE on STN DUPLICATE 12

94254452. PubMed ID: 7515130. Mitochondrial schwannopathy and peripheral myelinopathy in a rabbit model of dideoxycytidine neurotoxicity. Anderson T D; Davidovich A; Feldman D; Sprinkle T J; Arezzo J; Brosnan C; Calderon R O; Fossom L H; DeVries J T; **DeVries G H**. (Department of Toxicology and Pathology, Hoffmann-La Roche Inc., Nutley, New Jersey.) Laboratory investigation; a journal of technical methods and pathology, (1994 May) 70 (5) 724-39. Journal code: 0376617. ISSN: 0023-6837. Pub. country: United States. Language: English.

AB BACKGROUND: The reverse transcriptase inhibitor, 2',3'-dideoxycytidine (ddC), causes a dose-limiting peripheral neuropathy in humans, the mechanism of which is unknown. Rabbits given ddC develop peripheral myelinopathy and axonopathy, but it has not been determined if either the myelin or axonal changes are primary or if they occur concurrently. EXPERIMENTAL DESIGN: To characterize sequential development of the ddC-induced neuropathy, 40 rabbits were given either vehicle or ddC by oral intubation at a dose of 35 mg/kg per day for 24 weeks. Electrophysiologic studies, pathologic examination of peripheral and central nervous system and skeletal muscle, and biochemical analysis of the sciatic nerve were performed at baseline (electrophysiology only) and after 8, 12, 16, 20, and 24 weeks of **treatment**. RESULTS: Neuropathologic changes in peripheral nerves were first evident at 16 weeks and were more pronounced at 20 and 24 weeks; onset of paresis occurred at week 20, whereas clear electrophysiologic deficits were seen only at week 24. Electrophysiologic changes were prolonged F-waves (measure of proximal motor conduction) and minor changes in distal conduction measurements. Pathologic changes included myelin splitting, intramyelinic edema, demyelination, and remyelination of the largest diameter nerve fibers in the ventral root and sciatic nerve. Axonal degeneration and reduction in axonal diameter were seen. Enlarged mitochondria with abnormal ultrastructure were present in Schwann cells of those animals with a myelinopathy. Mitochondrial abnormalities or other signs of degeneration were not seen in neurons of the dorsal root ganglia or in skeletal muscle. Significant changes were not present in myelin protein composition, myelin lipid composition, or activity of the myelin-specific enzyme 2',3'-cyclic nucleotide 3'-phosphohydrolase. Major reductions in levels of protein zero (P0, the homophilic adhesion protein of myelin) were not seen; however, the turnover rate of P0 was reduced as P0 messenger RNA expression in ddC-treated sciatic nerves decreased to 30 to 50% of control values. CONCLUSIONS: The peripheral neuropathy caused by ddC in rabbits is characterized as a myelinopathy of the proximal portion of the nerve fibers and as an axonopathy involving both proximal and distal fibers. The myelinopathy was associated with enlarged and abnormally shaped mitochondria in Schwann cells and is consistent with an effect of ddC on structure and function of Schwann cell mitochondria. Altered Schwann cell metabolism was evident by reduced levels of P0 messenger RNA, loss of homophilic myelin adhesion at the intraperiod line, and subsequent intramyelinic edema. Because axonal degeneration occurred concurrently with the myelin changes, it could not be determined if axonal changes were secondary to serve myelinic edema or if they represented a primary effect of ddC on neurons.

L35 ANSWER 40 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

94:364424 The Genuine Article (R) Number: NQ264. GLUCOCORTICOIDS ENHANCE THE POTENCY OF SCHWANN-CELL MITOGENS. NEUBERGER T J; KALIMI O; REGELSON W; KALIMI M; **DEVRIES G H (Reprint)**. VIRGINIA COMMONWEALTH UNIV, MED

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Previous studies have documented that cultured Schwann cells require serum-containing medium to respond maximally to mitogens. We now report that Schwann cells are able to proliferate to a mitogenic response in a serum-free defined medium termed oligodendrocyte defined media (ODM). Glucocorticoids are the essential component of ODM which allow Schwann cell proliferation in the serum-free medium. Charcoal **treatment** of the fetal calf serum decreases the mitogenic potency of the axolemma-enriched fraction (AEF) by 50%. The addition of 2 mu M hydrocortisone to charcoal-treated fetal calf serum restores 75% of the lost mitogenicity. These observations are consistent with the view that glucocorticoids present in fetal calf serum are potent co-mitogens essential for AEF-induced Schwann cell proliferation. The synthetic glucocorticoid, dexamethasone, is a more potent co-mitogen than hydrocortisone, with a maximal effect at concentrations less than 10 nM. In contrast, other steroids including aldosterone, progesterone, testosterone, and 17 beta-estradiol have no effect on enhancing the mitogenic response of Schwann cells to the AEF. The glucocorticoid antagonists RU 486 and dehydroepiandrosterone (DHEA), but not the antiestrogenic compound tamoxifen, block AEF-induced Schwann cell proliferation. These results suggest that glucocorticoid-induced Schwann cell proliferation is mediated through a glucocorticoid receptor (GR) mechanism. We detected immunoreactivity to the GR in the cytoplasm, but not in the nuclei of Schwann cells grown in ODM lacking dexamethasone. The addition of 100 nM dexamethasone to these cultures resulted in immunoreactivity in the nucleus. This data suggests that glucocorticoids working through the GR are potent co-mitogens for Schwann cell proliferation. (C) 1994 Wiley-Liss, Inc.

L35 ANSWER 41 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
93:353476 The Genuine Article (R) Number: LE170. SEXUAL-DIFFERENTIATION OF VASOPRESSIN PROJECTIONS OF THE BED NUCLEUS OF THE STRIA TERMINALS AND MEDIAL AMYGDALOID NUCLEUS IN RATS. WANG Z X (Reprint); BULLOCK N A; **DEVRIES G J**. UNIV MASSACHUSETTS, DEPT PSYCHOL, PROGRAM NEUROSCI & BEHAV, AMHERST, MA, 01003 (Reprint). ENDOCRINOLOGY (JUN 1993) Vol. 132, No. 6, pp. 2299-2306. ISSN: 0013-7227. Pub. country: USA. Language: ENGLISH.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The vasopressin-immunoreactive (AVP-ir) projections of the bed nucleus of the stria terminalis (BST) and medial amygdaloid nucleus (MA) are much denser in males than in females even if males and females are treated with similar amounts of testosterone. Previous studies have established that testosterone influences AVP-ir projections during development, but not whether these effects of testosterone were permanent. This study tested the effects of various hormonal manipulations during development on the ability of testosterone to influence the AVP immunostaining in cells of the BST and MA and of fibers in the lateral septum of adult rats.

In the first experiment, male rats that were castrated at 3 months of age (control males) had more AVP-ir cells in the BST and a higher density of AVP-ir fibers in the lateral septum than neonatally castrated male rats, whose cell numbers and fiber density did not differ from female rats that were ovariectomized neonatally or at 3 months of age (control females). This suggested that testicular secretions influence sexual differentiation of AVP-ir fiber pathways after birth. The second experiment showed that males castrated at the day of birth or at 1 week after birth had less AVP-ir cells in the BST and MA and a lower AVP-ir

[illegible] gonadectomized male and female rats and fully restored the number of AVP-ir cells in the BST of neonatally castrated males. Combined, these data suggest that testosterone levels around the seventh postnatal day determine the sexual differentiation of AVP-ir projections to the lateral septum.

L35 ANSWER 42 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
93:738796 The Genuine Article (R) Number: MK991. TESTOSTERONE EFFECTS ON PATERNAL BEHAVIOR AND VASOPRESSIN IMMUNOREACTIVE PROJECTIONS IN PRAIRIE VOLES (MICROTUS-OCHROGASTER). WANG Z X (Reprint); **DEVRIES G J.** UNIV MASSACHUSETTS, DEPT PSYCHOL, NEUROSCI & BEHAV PROGRAM, AMHERST, MA, 01003 (Reprint). BRAIN RESEARCH (17 DEC 1993) Vol. 631, No. 1, pp. 156-160 . ISSN: 0006-8993. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Castration reduced paternal responsiveness of male prairie voles (Microtus ochrogaster). Castration also reduced the number of vasopressin immunoreactive (AVP-ir) cells in the bed nucleus of the stria terminalis (BST) and medial amygdaloid nucleus (MA), as well as the density of AVP-ir fibers in the lateral septum. Testosterone **treatment** of castrated voles prevented these changes. The similarities in the effects of the hormonal manipulations on paternal responsiveness and AVP immunoreactivity provide further support for the hypothesis that AVP-ir projections of the BST and MA are implicated in paternal behavior.

L35 ANSWER 43 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN
1993:425450 Document No. 119:25450 Increased PO glycoprotein gene expression in primary and transfected rat Schwann cells after **treatment** with axolemma-enriched fraction. Knight, R. M.; Fossom, L. H.; Neuberger, T. J.; Attema, B. L.; Tennekoon, G.; Bharucha, V.; **DeVries, G. H.** (Dep. Biochem. Mol. Biophys., Med. Coll. Virginia, Richmond, VA, 23298-0614, USA). Journal of Neuroscience Research, 35(1), 39-45 (English) 1993. CODEN: JNREDK. ISSN: 0360-4012.
AB To elucidate the role of axonal plasma membrane factors in the differentiation of Schwann cells, the authors investigated the effect of an axolemma-enriched fraction (AEF) isolated from myelinated central nervous system tissue on the expression of PO glycoprotein, the major glycoprotein in peripheral myelin, in primary rat Schwann cells (PSC) isolated from sciatic nerve, as well as in a transfected rat Schwann cell line (TSC). AEF increased PO-mRNA levels in PSC and TSC in a concentration-dependent manner, producing a maximal induction of nearly 2-fold after 48 h of **treatment.** A similar induction of PO mRNA was elicited in TSC by the cAMP-activating agents 8-bromo-cAMP and forskolin, which have been shown to induce myelin proteins in PSC. In addition to inducing PO mRNA, AEF and forskolin also increased the amount of PO protein in TSC, as indicated by increased PO-immunoreactive staining. However, in TSC, axolemma caused no increase in expression of CAT linked to a PO promoter while forskolin caused a marked increase in the expression from the PO promoter. These results suggest that AEF, in contrast to forskolin, does not regulate PO-mRNA expression at the level of transcriptional activity. These in vitro systems may be useful for the study of axolemmal factors that induce Schwann cell differentiation.

L35 ANSWER 44 OF 50 MEDLINE on STN DUPLICATE 13
93287151. PubMed ID: 7685396. Increased P0 glycoprotein gene expression in primary and transfected rat Schwann cells after **treatment** with axolemma-enriched fraction. Knight R M; Fossom L H; Neuberger T J; Attema B L; Tennekoon G; Bharucha V; **DeVries G H.** (Department of

axolemma enriched fraction (AEF) isolated from myelinated CNS tissue on the expression of P0 glycoprotein, the major glycoprotein in peripheral myelin, in primary rat Schwann cells (PSC) isolated from sciatic nerve, as well as in a transfected rat Schwann cell line (TSC). AEF increased PO-mRNA levels in PSC and TSC in a concentration-dependent manner, producing a maximal induction of nearly twofold after 48 hr of **treatment**. A similar induction of P0 mRNA was elicited in TSC by the cAMP-activating agents 8-bromo-cAMP and forskolin, which have been shown to induce myelin proteins in PSC. In addition to inducing P0 mRNA, AEF and forskolin also increased the amount of P0 protein in TSC, as indicated by increased P0-immunoreactive staining. However, in TSC, axolemma caused no increase in expression of CAT linked to a P0 promoter while forskolin caused a marked increase in the expression from the P0 promoter. These results suggest that AEF, in contrast to forskolin, does not regulate P0-mRNA expression at the level of transcriptional activity. These in vitro systems may be useful for the study of axolemmal factors that induce Schwann cell differentiation.

L35 ANSWER 45 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
93:241158 The Genuine Article (R) Number: KX144. PROSPECTIVE INVIVO STUDY OF CHLOROQUINE RESISTANCE OF PLASMODIUM-FALCIPARUM IN ZAMBIAN UNDER-FIVES. SCHREUDER H W R; WOLTERS F L; **DEVRIES G**; WETSTEYN J C F M (Reprint). UNIV AMSTERDAM, ACAD MED CTR, DEPT INFECT DIS & TROP MED, MEIBERGDREEF, 1105 AZ AMSTERDAM, NETHERLANDS; OUR LADYS HOSP, CHILONGA, ZAMBIA. TROPICAL AND GEOGRAPHICAL MEDICINE (1993) Vol. 45, No. 1, pp. 15-17. ISSN: 0041-3232. Pub. country: NETHERLANDS; ZAMBIA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Zambian under-fives with malaria were selected on a positive thick blood smear for Plasmodium falciparum of at least 1000 parasites/mul on the day of admission. During a chloroquine course, daily follow-up of Parasitaemia was performed. Bloodsamples were taken on day 0 and day 3 to measure chloroquine levels before admission and after **treatment**. Eighty four patients were evaluated in this study. Forty eight patients did not meet all criteria. Thirty six patients met all criteria, of which 16 (44.5%) patients were infected with sensitive strains (S) and 20 (55.5%) with resistant strains (R) of P.falciparum.

L35 ANSWER 46 OF 50 MEDLINE on STN DUPLICATE 14
89068008. PubMed ID: 2908892. Mitogenic effect of axolemma-enriched fraction on cultured oligodendrocytes. Chen S J; **DeVries G H.** (Department of Biochemistry and Molecular Biophysics, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298-0614.) Journal of neurochemistry, (1989 Jan) 52 (1) 325-7. Journal code: 2985190R. ISSN: 0022-3042. Pub. country: United States. Language: English.
AB An in vitro system has been devised to study the mitogenic effect of axolemma on cultured oligodendrocytes. Addition of axolemma-enriched fraction to cultured oligodendrocytes results in a dose-dependent mitotic response with an 11-fold stimulation at a membrane concentration of 200 micrograms/ml. The interaction between oligodendrocytes and axolemma is specific, as myelin-enriched fraction, astrocyte membrane, and red blood cell membrane showed little or no effect on the oligodendroglial proliferation under similar conditions. In addition, cultured astrocytes were tested with the same axolemma membrane, and no mitotic stimulation was observed. The mitogenicity of AEF membrane on cultured oligodendrocytes is sensitive to heat and trypsin **treatment**, suggesting that the axolemma mitogen may be a protein.

Medical College of Virginia, Virginia Commonwealth University, Richmond 23298.) Journal of neuroscience research, (1989 Mar) 22 (3) 283-8. Journal code: 7600111. ISSN: 0360-4012. Pub. country: United States. Language: English.

AB **Treatment** of axolemma with pH 9 buffer results in a pellet enriched two-fold in the mitogen for cultured Schwann cells. Heparitinase **treatment** releases 8% of the mitogen into solution, while heparin selectively solubilizes the mitogen, resulting in an extract which has a specific mitogenic activity approximately 2.5 times greater than the mitogenicity of the starting axolemma membrane. These data support a model in which the axolemmal mitogen is a positively charged molecule associated with negatively charged sulfated proteoglycans.

L35 ANSWER 48 OF 50 MEDLINE on STN DUPLICATE 16

88061452. PubMed ID: 3681350. Morphological and proliferative responses of cultured Schwann cells following rapid phagocytosis of a myelin-enriched fraction. Bigbee J W; Yoshino J E; **DeVries G H.** (Department of Anatomy, Medical College of Virginia, Richmond 23298.) Journal of neurocytology, (1987 Aug) 16 (4) 487-96. Journal code: 0364620. ISSN: 0300-4864. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Cultured Schwann cells were found to phagocytose exogenously applied myelin membranes within 1 h. However, the resulting proliferative response required an additional 9 h of incubation. **Treatment** with ammonium chloride, a lysosomal inhibitor, delayed the appearance of the proliferative response to the myelin membranes by 12 h. Processing of myelin within the Schwann cells was followed by the appearance of immunocytochemically detectable myelin basic protein which was first visible at 4 h. Similar to the proliferative response, the appearance of immunoreactive material was delayed by the addition of ammonium chloride. Schwann cells were observed initially to ingest myelin fragments at their distal-most tips after which time the myelin phagosomes collected in the perinuclear region and fused with lysosomes. Phagocytic Schwann cells had a notable increase in Golgi membranes and microfilaments and contained widely dilated, rough endoplasmic reticulum cisternae. In purified cell cultures, Schwann cells phagocytosed myelin slower than macrophages, but displayed phagocytic abilities much greater than fibroblasts. The ability of cultured Schwann cells to phagocytose myelin rapidly suggests that these cells may aid in the breakdown and removal of myelin during Wallerian degeneration. These data further confirm the mitogenic effect of myelin and its possible role during nerve regeneration.

L35 ANSWER 49 OF 50 MEDLINE on STN DUPLICATE 17

86061756. PubMed ID: 3934342. Differential proliferative responses of cultured Schwann cells to axolemma and myelin-enriched fractions. II. Morphological studies. Meador-Woodruff J H; Yoshino J E; Bigbee J W; Lewis B L; **Devries G H.** Journal of neurocytology, (1985 Aug) 14 (4) 619-35. Journal code: 0364620. ISSN: 0300-4864. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Axolemma-enriched and myelin-enriched fractions were prepared from bovine CNS white matter and conjugated to fluorescein isothiocyanate (FITC). Both unlabelled and FITC-labelled axolemma and myelin were mitogenic for cultured rat Schwann cells. **Treatment** of Schwann cells with the FITC-labelled mitogens for up to 24 h resulted in two distinct morphological appearances. FITC-myelin-treated cells were filled with numerous round, fluorescent-labelled intracellular vesicles, while FITC-axolemma-treated cells appeared to be coated with a patchy, ill-defined fluorescence, primarily concentrated around the cell body but

chloride and chloroquine, was evaluated. The mitogenicity of myelin was reduced 70-80% by these agents whereas the mitogenicity of axolemma was not significantly altered under these conditions. These results suggest that axolemma and myelin stimulate the proliferation of cultured Schwann cells by different mechanisms. Myelin requires endocytosis and lysosomal processing for expression of its mitogenic signal; in contrast, the mitogenicity of axolemma may be transduced at the Schwann cell surface.

L35 ANSWER 50 OF 50 MEDLINE on STN DUPLICATE 18
84256813. PubMed ID: 6331451. Cyclic AMP and calcium as potential mediators of stimulation of cultured Schwann cell proliferation by axolemma-enriched and myelin-enriched membrane fractions. Meador-Woodruff J H; Lewis B L; **DeVries G H.** Biochemical and biophysical research communications, (1984 Jul 18) 122 (1) 373-80. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.
AB The roles of cyclic AMP and calcium in the transduction of the mitogenic effects of central nervous system axolemma and myelin-enriched fractions on cultured Schwann cells were examined. Cyclic AMP levels were not elevated in axolemma or myelin-stimulated Schwann cells, but were increased when stimulated with cholera toxin, an adenyl cyclase activator. The mitogenicity of axolemma and myelin was markedly reduced by 2.5 mM citrate, a calcium chelator, and 10 uM trifluoroperazine, an inhibitor of calmodulin. **Treatment** of Schwann cells with several tumor-promoting phorbol esters caused significant enhancement of the mitogenicity of the axolemma and myelin preparations. These data suggest that the mitogenic effects of axolemma and myelin are not mediated by cyclic AMP, but may be mediated by calcium ions.

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=> s APT analog
L37           1 APT ANALOG

=> s ATP analog
L38        5672 ATP ANALOG

=> s l38 and "MAE106"
L39           0 L38 AND "MAE106"

=> s l38 and "3(2,4-dihydroxy-benzylidene)-1,3-dihydroindol-2one"
L40           0 L38 AND "3(2,4-DIHYDROXY-BENZYLIDENE)-1,3-DIHYDROINDOL-2ONE"

=> s l38 and kinase inhibitor
L41         103 L38 AND KINASE INHIBITOR

=> s l41 and tyrosine kinase
L42          20 L41 AND TYROSINE KINASE

=> dup remove l42
PROCESSING COMPLETED FOR L42
L43          11 DUP REMOVE L42 (9 DUPLICATES REMOVED)

=> d l43 1-11 cbib abs

L43  ANSWER 1 OF 11  SCISEARCH  COPYRIGHT 2004 THOMSON ISI on STN
2002:834841   The Genuine Article (R) Number: 602PY. Inhibitor scaffolds as new
     allele specific kinase substrates.  Kraybill B C; Elkin L L; Blethrow J D;
     Morgan D O; Shokat K M (Reprint). Univ Calif San Francisco, Dept Mol &
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PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.
ISSN: 0002-7863. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The elucidation of protein kinase signaling networks is challenging due to the large size of the protein kinase superfamily (> 500 human kinases). Here we describe a new class of orthogonal triphosphate substrate analogues for the direct labeling of analogue-specific kinase protein targets. These analogues were constructed as derivatives of the Src family **kinase inhibitor** PP1 and were designed based on the crystal structures of PP1 bound to HCK and N-6-(benzyl)-ADP bound to c-Src (T338G). 3-Benzylpyrazolopyrimidine triphosphate (3-benzyl-PPTP) proved to be a substrate for a mutant of the MAP kinase p38 (p38-T106G/A157L/L167A). 3-Benzyl-PPTP was preferred by v-Src (T338G) (k(cat)/K-M = 3.2 x 10(6) min(-1) M-1) over ATP or the previously described ATP analogue, N-6 (benzyl) ATP. For the kinase CDK2 (F80G)/cyclin E, 3-benzyl-PPTP demonstrated catalytic efficiency (k(cat)/K-M = 2.6 x 10(4) min(-1) M-1) comparable to ATP (k(cat)/K-M = 5.0 x 10(4) min(-1) M-1) largely due to a significantly better K-M (6.4 muM vs 530 muM). In kinase protein substrate labeling experiments both 3-benzyl-PPTP and 3-phenyl-PPTP prove to be over 4 times more orthogonal than N-6-(benzyl)-ATP with respect to the wild-type kinases found in murine spleenocyte cell lysates. These experiments also demonstrate that [gamma-P-32]-3-benzyl-PPTP is an excellent phosphodonor for labeling the direct protein substrates of CDK2 (F80G)/E in murine spleenocyte cell lysates, even while competing with cellular levels (4 mM) of unlabeled ATP. The fact that this new more highly orthogonal nucleotide is accepted by three widely divergent kinases studied here suggests that it is likely to be generalizable across the entire kinase superfamily.

L43 ANSWER 2 OF 11 EMBASE
on STN DUPLICATE 1

2002293043 EMBASE K252a inhibits the oncogenic properties of Met, the HGF receptor. Morotti A.; Mila S.; Accornero P.; Tagliabue E.; Ponzetto C.. C. Ponzetto, Department of Anatomy, Pharmacology and Forensic Medicine, University of Turin, C.so Massimo d'Azeglio 52, 10126 Turin, Italy. carola.ponzetto@unito.it. Oncogene 21/32 (4885-4893) 25 Jul 2002. Refs: 50.
ISSN: 0950-9232. CODEN: ONCNES. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The **ATP analog** K252a is a potent inhibitor for receptor **tyrosine kinases** of the Trk family. Here we show that nanomolar concentrations of K252a prevent HGF-mediated scattering in MLP-29 cells (30 nM), reduce Met-driven proliferation in GTL-16 gastric carcinoma cells (100 nM), and cause reversion in NIH3T3 fibroblasts transformed by the oncogenic form of the receptor, Tpr-Met (75 nM). K252a inhibits Met autophosphorylation in cultured cells and in immunoprecipitates and prevents activation of its downstream effectors MAPKinase and Akt. Interestingly, K252a seems to be more effective at inhibiting the mutated form of Met (M1268T) found in papillary carcinoma of the kidney than the wild type receptor. Pretreatment of both Tpr-Met-transformed NIH3T3 fibroblasts and of GTL-16 gastric carcinoma cells with K252a results in loss of their ability to form lung metastases in nude mice upon injection into the caudal vein. These observations suggest that K252a derivatives, which are active in vivo as anti-cancer drugs in models of Trk-driven malignancies, should also be effective for treatment of Met-mediated tumors.

--- **tyrosine kinase** has been genetically validated in Src -/- mice as a critical signal transduction protein for bone resorption by osteoclasts and, more recently, bone formation by osteoblasts. The 3D structure of Src **tyrosine kinase** has been determined relative to its noncatalytic (SH2 and SH3) and catalytic domains, including complexes thereof with peptidic ligands or **ATP analogs**. Structure-based design of Src **tyrosine kinase inhibitors** have been focused on both the noncatalytic and catalytic domains to identify lead compds. with promising in vitro and in vivo biol. activities in models of bone diseases. Our drug discovery strategies have resulted in several series of promising lead compds. that exemplify various nonpeptide templates and incorporate functional groups that target bone tissue to confer biol. selectivity in vivo. Novel, potent, and selective Src **tyrosine kinase inhibitors** have been developed that exhibit in vivo efficacy in animal models of bone diseases.

L43 ANSWER 4 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

2001:313558 Document No.: PREV200100313558. Unexpected effects of N-terminal mutations on catalytic activity of JAK3: Structural implication for Janus kinases. Zhou, Yongjie [Reprint author]; Changelian, Paul S.; O'Shea, John J. [Reprint author]. NIAMS, NIH, 10 Center Dr., Bethesda, MD, 20892-1820, USA. FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1015. print. Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638. Language: English.

AB Mutations of Jak3 result in autosomal severe combined immunodeficiency (SCID). Despite its importance, however, the structure of Jaks is not well understood. The Jaks are characterized by seven Janus homology domains (JH1-7H7): a C-terminal **tyrosine kinase** domain (JH1), a pseudokinase domain (JH2), and JH4-JH7 domains which are required for Jak3 binding to receptor gamma c subunit. To gain insight into Jak3 structure, we examined the catalytic activity of several naturally occurring Jak3 mutations from SCID patients and analyzed the function of these mutants in several ways. We performed kinase assays on immunoprecipitated Jak3 from patient B cells or on Jak3 mutants created by site-directed mutagenesis and overexpressed in COS-7 cells. Surprisingly, all patient-derived point mutations in Jak3 N-terminus abrogated its kinase activity. We next investigated if the abrogation in kinase activity was due to the inability to bind ATP. To this end, we used an **ATP analog**, 5'-p-fluorosulfonylbenzoyl adenosine (FSBA), which covalently binds kinase domain. All mutants failed to bind FSBA, suggesting that mutations in its N-terminus interfere with the conformation of its kinase domain. There are a few examples of mutations outside a kinase domain that abrogate catalytic activity, such as mutations at a pleckstrin homology domain or at SH2 domain. We hypothesized that the structure of the Jaks might be such that the N-terminus interacts with the kinase domain. To test this, we evaluated the binding ability of Jak3 to gamma c in the presence of a **kinase inhibitor**, staurosporine, which is known to bind in the ATP-binding site. Interestingly, staurosporine not only inhibited Jak3 kinase activity, but also disrupted the interaction between Jak3 and gamma c. Taken together, our data support a model in which point mutations at Jak3 N-terminus distort the proper intramolecular interactions between its N-terminal and kinase domains. This leads to a catalytic inactive conformation and inability to bind ATP, and thus underlies the disease

(Reprint); UNIV OTTAWA, LOEB HLTH RES INST, OTTAWA, ON K1Y 4E9, CANADA. BIOCHIMICA ET BIOPHYSICA ACTA-BIOMEMBRANES (29 SEP 2000) Vol. 1468, No. 1-2, pp. 63-72. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0005-2736. Pub. country: CANADA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The effects of inhibitors of protein **tyrosine kinases** (PTKs) on the Cl- current (I-Cl(vol)) through volume-regulated anion/chloride (VRAC) channels whilst manipulating cellular ATP have been studied in mouse fibroblasts using the whole-cell patch clamp technique. Removal of ATP from the pipette-filling solution prevented activation of the current during osmotic cell swelling and when the volume of patched cells was increased by the application of positive pressure through the patch pipette to achieve rates exceeding 100%/min. Equimolar substitution of ATP in the pipette solution with its non-hydrolyzable analogs, adenosine 5'-O-(3-thiotriphosphate) (ATP gamma S) or adenylyl-(beta,gamma-methylene)-diphosphonate (AMP-PCP), not only supported activation of the current but also maintained its amplitude. The PTK inhibitors, tyrphostins A25, B46, 3-amino-2,4-dicyano-5-(4-hydroxyphenyl)penta-2,4-dienonitrile and genistein (all at 100 mu M), inhibited I-Cl(vol) in a time-dependent manner, Tyrphostin A1, which does not inhibit PTK activity, did not affect the current amplitude. The PTK inhibitors also inhibited I-Cl(vol) under conditions where ATP in the pipette was substituted with ATP gamma S or AMP-PCP. We conclude that in mouse fibroblasts ATP has a dual role in the regulation of the current: it is required for protein phosphorylation to keep VRAC channels operational and, through non-hydrolytic binding, determines the magnitude of I-Cl(vol). We also suggest that tyrosine-specific protein kinases and phosphatases exhibit an interdependent involvement in the regulation of VRAC channels. (C) 2000 Elsevier Science B.V. All rights reserved.

L43 ANSWER 6 OF 11 MEDLINE on STN DUPLICATE 2

1999332673. PubMed ID: 10404594. Structural analysis of the lymphocyte-specific kinase Lck in complex with non-selective and Src family selective **kinase inhibitors**. Zhu X; Kim J L; Newcomb J R; Rose P E; Stover D R; Toledo L M; Zhao H; Morgenstern K A. (Kinetix Pharmaceuticals, Inc., Medford, MA 02155, USA.. zhu@kinetixpharm.com) . Structure with Folding & design, (1999 Jun 15) 7 (6) 651-61. Journal code: 100889329. ISSN: 0969-2126. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: The lymphocyte-specific kinase Lck is a member of the Src family of non-receptor **tyrosine kinases**. Lck catalyzes the initial phosphorylation of T-cell receptor components that is necessary for signal transduction and T-cell activation. On the basis of both biochemical and genetic studies, Lck is considered an attractive cell-specific target for the design of novel T-cell immunosuppressants. To date, the lack of detailed structural information on the mode of inhibitor binding to Lck has limited the discovery of novel Lck inhibitors. RESULTS: We report here the high-resolution crystal structures of an activated Lck kinase domain in complex with three structurally distinct ATP-competitive inhibitors: AMP-PNP (a non-selective, non-hydrolyzable **ATP analog**); staurosporine (a potent but non-selective protein **kinase inhibitor**); and PP2 (a potent Src family selective protein **tyrosine kinase inhibitor**). Comparison of these structures reveals subtle but important structural changes at the

kinases by making additional contacts in a deep, hydrophobic pocket adjacent to the ATP-binding site; the amino acid composition of this pocket is unique to Src family kinases. The structures of these Lck complexes offer useful structural insights as they demonstrate that kinase selectivity can be achieved with small-molecule inhibitors that exploit subtle topological differences among protein kinases.

L43 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
1998:793407 Document No. 130:164704 Bivalent Inhibitors of Protein **Tyrosine Kinases**. Profit, Adam A.; Lee, Tae Ryong; Lawrence, David S. (Department of Biochemistry The Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, 10461, USA). Journal of the American Chemical Society, 121(2), 280-283 (English) 1999. CODEN: JACSAT. ISSN: 0002-7863. Publisher: American Chemical Society.

AB The majority of protein **kinase inhibitors** described to date are **ATP analogs**. However, the selectivity of these species is highly suspect, given the enormous number of ATP-dependent processes that transpire in living cells. Inhibitors that target the protein binding site do not suffer from this disadvantage but exhibit comparatively low inhibitory activity. An alternative approach for the design of protein **tyrosine kinase inhibitors** is described herein. We have constructed species that simultaneously bind to the active site and the SH2 domain of the Src kinase. Since the region of the inhibitor that assocs. with the SH2 domain coordinates with relatively high affinity, the overall effect is a substantial enhancement in inhibitory potency (230-fold). This design element offers a strategy to overcome the otherwise poor efficacy of peptide-based protein **tyrosine kinase inhibitors**.

L43 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
1998:486707 Document No. 129:198440 Role of tyrosine phosphorylation in leptin activation of ATP-sensitive K+ channels in the rat insulinoma cell line CRI-G1. Harvey, J.; Ashford, M. L. J. (Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, AB25 2ZD, UK). Journal of Physiology (Cambridge, United Kingdom), 510(1), 47-61 (English) 1998. CODEN: JPHYA7. ISSN: 0022-3751. Publisher: Cambridge University Press.

AB Using whole-cell and cell-attached recording configurations, the role of phosphorylation in leptin activation of ATP-sensitive K+ (KATP) channels was examined in the rat CRI-G1 insulinoma cell line. Whole-cell current clamp recordings demonstrated that, following dialysis with the non-hydrolyzable **ATP analog** 5'-adenylylimidodiphosphate (AMP-PNP; 3-5 mM), the leptin-induced hyperpolarization and increase in K+ conductance were completely inhibited. Under current clamp conditions, application of the broad-spectrum protein **kinase inhibitor** H-7 (10 μM) had no effect on the resting membrane potential or slope conductance of CRI-G1 insulinoma cells and did not occlude the actions of leptin. Application of the **tyrosine kinase inhibitors** genistein (10 μM), tyrphostin B42 (10 μM) and herbimycin A (500 nM) all resulted in activation of KATP channels. In cell-attached recordings, the presence of tyrphostin B42 (10 μM) in the pipet solution activated tolbutamide-sensitive KATP channels in CRI-G1 cells. In contrast, the inactive analogs of genistein and tyrphostin B42 were without effect. The serine/threonine-specific protein phosphatase inhibitors okadaic acid (50 nM) and cyclosporin A (1 μM) did not prevent or reverse leptin

by tyrphostin B42.

L43 ANSWER 9 OF 11 MEDLINE on STN DUPLICATE 3
96165700. PubMed ID: 8574217. Tyrphostin induces non-apoptotic programmed cell death in colon tumor cells. Szende B; Keri G; Szegedi Z; Benedeczky I; Csikos A; Orfi L; Gazit A. (1st Institute of Pathology and Experimental Cancer Research, Hungarian Academy of Sciences, Semmelweis University of Medicine, Budapest, Hungary.) Cell biology international, (1995 Nov) 19 (11) 903-11. Journal code: 9307129. ISSN: 1065-6995. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The programmed cell death inducing effect of the EGF receptor **tyrosine kinase inhibitor** alpha-cyano-3,4-dihydroxycinnamthioamide (AG213) was investigated in vitro on HT-29 human colon tumor. AG213 at concentrations between 45 to 450 microM blocks the proliferation of HT-29 cells. Morphological findings suggest that the selective **tyrosine kinase inhibitor** AG213 induces Clarke III type (non-lysosomal vesiculate cytoplasmic) programmed cell death; unlike **ATP analog** non-selective **tyrosine kinase inhibitors** like Genistein which were found to induce apoptosis. Cycloheximide and Actinomycin-D reduced the effect of AG213 pointing to the fact that protein and RNA synthesis are also needed for this form of cell death. Acid phosphatase activity was found in the Golgi and in the newly formed intracytoplasmic vacuoles 3 hours after AG213 treatment which disappeared by 6 hours. The induction of Clarke III cell death by **tyrosine kinase inhibitors** may open a new modality to selective killing of tumor cells.

L43 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
1995:562431 Document No. 123:6567 Potential role of protein phosphorylation in GTP-γ-S-dependent activation of phospholipase D. Inoue, Hiroo; Shimooku, Kiyoshi; Akisue, Toshihiro; Nakamura, Shun-ichi (Dep. Biochem., Kobe Univ. Sch. Med., Kobe, 650, Japan). Biochemical and Biophysical Research Communications, 210(2), 542-8 (English) 1995. CODEN: BBRCA9. ISSN: 0006-291X. Publisher: Academic.

AB Mammalian phospholipase D (PLD) is known to require nearly absolutely guanosine 5'-O-3-thiotriphosphate (GTP-γ-S) and a small G-protein for its activation. In streptolysin-O-permeabilized HL-60 cells, phorbol ester or diacylglycerol enhanced greatly this PLD activation in the presence of ATP-Mg2+. The nonhydroylzable **ATP analog** was inactive. This phorbol-ester-induced PLD activation was completely counteracted not only by protein kinase C (PKC) inhibitors but also by **tyrosine kinase inhibitors**. In cell-free lysates, the GTP-γ-S-dependent activation of PLD was stimulated by ATP-Mg2+. This stimulation by ATP-Mg2+ did not respond to phorbol ester nor was it inhibited by PKC inhibitors, but was fully restrained by **tyrosine kinase inhibitors**. The results suggest that protein phosphorylation reactions by PKC and **tyrosine kinase** may take part, possibly in this order, in the small G-protein-coupled PLD activation.

L43 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
1996:120869 Document No. 124:166189 ATP-dependent inhibition of Ca2+-activated K+ channels in vascular smooth muscle cells by neuropeptide Y. Xiong, Zhigang; Cheung, Donald W. (Dep. of Pharmacology, Univ. of Ottawa Heart Inst., Ottawa, K1Y 4E9, Can.). Pfluegers Archiv, 431(1), 110-16 (English) 1995. CODEN: PFLUAM

substituted by the non-hydrolyzable **ATP analog** adenosine 5'-[β, γ-methylene]-triphosphate (AMP-PCP). NPY inhibited Ca2+-activated K+ channel activity when ATP was replaced by adenosine 5'-O-(3-thiotriphosphate) (ATP [γ-S]) and the inhibition was not readily reversed upon washing. Protein **kinase inhibitor** (1 μM), a specific inhibitor of cAMP-dependent protein kinase, had no significant effect on the inhibitory action of NPY. The effect of NPY on single-channel activity was inhibited by the **tyrosine kinase inhibitor** genistein (10 μM) but not by daidzein, an inactive analog of genistein. These observations suggest that the inhibition by NPY of Ca2+-activated K+ channels is mediated by ATP-dependent phosphorylation. The inhibitory effect of NPY was antagonized by the **tyrosine kinase inhibitor** genistein.

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=> s tyrosine kinase inhibitor
L44      25122 TYROSINE KINASE INHIBITOR

=> s l44 and VEGF receptor
L45        368 L44 AND VEGF RECEPTOR

=> s l45 and VEGFR-3
L46         21 L45 AND VEGFR-3

=> dup remove l46
PROCESSING COMPLETED FOR L46
L47         11 DUP REMOVE L46 (10 DUPLICATES REMOVED)

=> d l47 1-11 cbib abs

L47  ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2004 ACS on STN
2003:633416  Document No. 139:173786  Method for treating diseases associated
     with abnormal kinase activity.  Lyons, John; Rubinfeld, Joseph (Supergen,
     Inc., USA).  PCT Int. Appl. WO 2003065995 A2 20030814, 64 pp.  DESIGNATED
     STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
     CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM,
     HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
     LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC,
     SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
     ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF,
     CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML,
     MR, NE, NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN: PIXXD2.
     APPLICATION: WO 2003-US3537 20030206.  PRIORITY: US 2002-71849 20020207;
     US 2002-206854 20020726.
AB   Methods are provided for treating diseases associated with abnormal activity
     of kinases such as chronic myelogenous leukemia.  The method comprises:
     administering a DNA methylation inhibitor to the patient in
     therapeutically effective amount; and administering a kinase inhibitor such
     as imatinib mesylate to the patient in therapeutically effective amount,
     such that the in vivo activity of the kinase is reduced relative to that
     prior to the treatment.  The method can be used to treat cancer associated
     with abnormal activity of kinases such as phosphatidylinositol 3'-kinase
     (P13K), protein kinases including serine/threonine kinases such as Raf
     kinases, protein kinase kinases such as MEK, and tyrosine kinases such as
     those in the epidermal growth factor receptor family (EGFR),
     platelet-derived growth fa
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L47 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2003:780133 Document No. 140:174592 CEP-7055: a novel, orally active pan inhibitor of vascular endothelial growth factor receptor tyrosine kinases with potent antiangiogenic activity and antitumor efficacy in preclinical models. Ruggeri, Bruce; Singh, Jasbir; Gingrich, Diane; Angeles, Thelma; Albom, Mark; Chang, Hong; Robinson, Candy; Hunter, Kathryn; Dobrzanski, Pawel; Jones-Bolin, Susan; Aimone, Lisa; Klein-Szanto, Andres; Herbert, Jean-Marc; Bono, Francoise; Schaeffer, Paul; Casellas, Pierre; Bourie, Bernard; Pili, Roberto; Isaacs, John; Ator, Mark; Hudkins, Robert; Vaught, Jeffry; Mallamo, John; Dionne, Craig (Department of Oncology, Cephalon, Inc., West Chester, PA, 19380, USA). Cancer Research, 63(18), 5978-5991 (English) 2003. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB Inhibition of the vascular endothelial growth factor VEGF-**VEGF receptor** (VEGF-R) kinase axes in the tumor angiogenic cascade is a promising therapeutic strategy in oncol. CEP-7055 is the fully synthetic orally active N,N-di-Me glycine ester of CEP-5214, a C3-(isopropylmethoxy) fused pyrrolocarbazole with potent pan-VEGF-R kinase inhibitory activity. CEP-5214 demonstrates IC50 values of 18 nM, 12 nM, and 17 nM against human VEGF-R2/KDR kinase, VEGF-R1/FLT-1 kinase, and VEGF-R3/FLT-4 kinase, resp., in biochem. kinase assays. CEP-5214 inhibited VEGF-stimulated VEGF-R2/KDR autophosphorylation in human umbilical vein endothelial cells (HUVECs) with an IC 50 of .apprx.10 nM and demonstrated an equivalent inhibition of murine FLK-1 autophosphorylation in transformed SVR endothelial cells. Evaluation of the antiangiogenic activity of CEP-5214 revealed a dose-related inhibition of microvessel growth ex vivo in rat aortic ring explant cultures and in vitro on HUVEC capillary-tube formation on Matrigel at low nanomolar concns. The antiangiogenic activity of CEP-5214 in these bioassays was observed in the absence of apparent cytotoxicity. Single-dose p.o. or s.c. administration of CEP-7055 or CEP-5214 to CD-1 mice at 23.8 mg/kg/dose b.i.d. resulted in a reversible inhibition of VEGF-R2/FLK-1 phosphorylation in murine lung tissues. Administration p.o. of CEP-7055 at 2.57 to 23.8 mg/kg/dose b.i.d. resulted in dose-related redns. in neovascularization in vivo in porcine aortic endothelial cell (PAEC)-VEGF/basic fibroblast growth factor-Matrigel implants in nude mice (maximum, 82% inhibition), significant redns. in granuloma formation (30%) and granuloma vascularity (42%) in a murine chronic inflammation-induced angiogenesis model, and significant and sustained (6 h) inhibition of VEGF-induced plasma extravasation in rats, with an ED50 of 20 mg/kg/dose. Chronic p.o. administration of CEP-7055 at doses of 11.9 to 23.8 mg/kg/dose b.i.d. resulted in significant inhibition (50-90% maximum inhibition relative to controls) in the growth of a variety of established murine and human s.c. tumor xenografts in nude mice, including A375 melanomas, U251MG and U87MG glioblastomas, CALU-6 lung carcinoma, ASPC-1 pancreatic carcinoma, HT-29 and HCT-116 colon carcinomas, MCF-7 breast carcinomas, and SVR angiosarcomas. Significant antitumor efficacy was observed similarly against orthotopically implanted LNCaP human prostate carcinomas in male nude mice and orthotopically implanted renal carcinoma (RENCA) tumors in BALB/c mice, in terms of a significant reduction in the metastatic score and the extent of pulmonary metastases. These antitumor responses were associated with marked increases in tumor apoptosis, and significant redns. in intratumoral microvessel d. (CD34 and Factor VIII staining) of 22-38% relative to controls depending on the specific tumor xenograft. The antitumor efficacy of chronic CEP-7055 administration was independent of initial tumor volume (in the ASPC-1 pancreatic carcinoma model) and reversible on withdrawal of treatment. Chronic p.o. administration of CEP-7055 [illegible]

Endothelial Growth Factor Receptor **Tyrosine Kinase Inhibitors**: Structure-Activity Relationships for a Series of 9-Alkoxymethyl-12-(3-hydroxypropyl)indeno[2,1-a]pyrrolo[3,4-c]carbazole-5-ones and the Identification of CEP-5214 and Its Dimethylglycine Ester Prodrug Clinical Candidate CEP-7055. Gingrich, Diane E.; Reddy, Dandu R.; Iqbal, Mohamed A.; Singh, Jasbir; Aimone, Lisa D.; Angeles, Thelma S.; Albom, Mark; Yang, Shi; Ator, Mark A.; Meyer, Sheryl L.; Robinson, Candy; Ruggeri, Bruce A.; Dionne, Craig A.; Vaught, Jeffry L.; Mallamo, John P.; Hudkins, Robert L. (Departments of Medicinal Chemistry, Pharmacology, Biochemistry, Protein Expression, Oncology and Discovery Research, Cephalon, Inc., West Chester, PA, 19380, USA). Journal of Medicinal Chemistry, 46(25), 5375-5388 (English) 2003. CODEN: JMCMAR. ISSN: 0022-2623. Publisher: American Chemical Society.

AB A series of potent vascular endothelial growth factor R2 (VEGF-R2) **tyrosine kinase inhibitors** from a new indenopyrrolocarbazole template is reported. The structure-activity relationships for a series of 9-alkoxymethyl-12-(3-hydroxypropyl)indeno[2,1-a]pyrrolo[3,4-c]carbazole-5-ones revealed an optimal R9 substitution with ethoxymethyl 19 (VEGF-R2 IC50 = 4 nM) and isopropoxymethyl 21 (VEGF-R2 IC50 = 8 nM) being the most potent inhibitors in the series. The VEGF-R2 activity was reduced appreciably by increasing the size of the R9 alkoxy group or by α-Me branching adjacent to the ring. The combined R9 alkoxymethyl and N12 hydroxypropyl substitutions were required for potent VEGF-R2 activity, and the corresponding thioether analogs were weaker than their ether counterparts. Compound 21 (R9 isopropoxymethyl, CEP-5214) was identified as a potent, low-nanomolar pan inhibitor of human VEGF-R tyrosine kinases, displaying IC50 values of 16, 8, and 4 nM for VEGF-R1/FLT-1, VEGF-R2/KDR, and VEGF-R3/FLT-4, resp., with cellular activity equivalent to the isolated enzyme activity. Compound 21 exhibited good selectivity against numerous tyrosine and serine/threonine kinases including PKC, Tie2, TrkA, CDK1, p38, JNK, and IRK. To increase water solubility and oral bioavailability, the N,N-dimethylglycine ester 40 was prepared In pharmacokinetic studies in mice and rats, increased plasma levels of 21 were observed after oral administration of 40. Compound 21 demonstrated significant in vivo antitumor activity in numerous tumor models and was advanced into phase I clin. trials as the water-soluble N,N-dimethylglycine ester prodrug 40 (CEP-7055).

L47 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN

2003:503300 Document No. 139:240756 Functional evidence that vascular endothelial growth factor may act as an autocrine factor on human podocytes. Foster, Rebecca R.; Hole, Rachel; Anderson, Karen; Satchell, Simon C.; Coward, Richard J.; Mathieson, Peter W.; Gillatt, David A.; Saleem, Moin A.; Bates, David O.; Harper, Steven J. (Microvascular Research Laboratories, Department of Physiology, Preclinical Veterinary School, University of Bristol, Bristol, BS2 8EJ, UK). American Journal of Physiology, 284(6, Pt. 2), F1263-F1273 (English) 2003. CODEN: AJPHAP. ISSN: 0002-9513. Publisher: American Physiological Society.

AB Vascular endothelial growth factor (VEGF) is expressed by renal glomerular epithelial cells (podocytes) and is thought to be protective against nephrotoxic agents. VEGF has been shown to be an autocrine survival factor in neuropilin-1-pos., **VEGF receptor**-neg. breast carcinoma cells. Normal human podocytes are also known to express neuropilin-1, VEGF, and are VEGF-R2 neg. Here, we investigated whether a similar VEGF autocrine loop may exist in podocytes. Podocyte cytosolic calcium concentration ([Ca2+]i) was analyzed in primary cultured and

kinase inhibitor PTK787/ZK222584 abolished this reduction
VEGF increased podocyte [3H]-thymidine incorporation (3,349±283 cpm, control 2,364±301 cpm, P < 0.05) and cell number (4.5±0.7+104/mL, control 2.6±0.5+104/mL, P < 0.05) and decreased cytotoxicity (5.9±0.7%, control 12±3%, P < 0.05), whereas a monoclonal antibody to VEGF increased cytotoxicity. Electron microscopy of normal human glomeruli demonstrated that the glomerular VEGF is mostly podocyte cell membrane associated These results indicate that one of the functions of VEGF secreted from podocytes may be to act as an autocrine factor on calcium homeostasis and cell survival.

L47 ANSWER 5 OF 11 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 1

2004048554 EMBASE Modulation of signaling pathways by adaphostin (NSC-680410), an antileukemic **tyrosine kinase inhibitor**: The past, the present and recommendations for the future. Avramis V.I.. Dr. V.I. Avramis, #57, 4650 Sunset Blvd., Los Angeles, CA 90027, United States. vavramis@chla.usc.edu. Drugs of the Future 28/11 (1087-1102) 2003.
Refs: 99.
ISSN: 0377-8282. CODEN: DRFUD4. Pub. Country: Spain. Language: English. Summary Language: English.

AB Angiogenesis is involved in many physiological and pathological conditions including embryonic development, wound healing, menstrual cycle, chronic inflammation and the development of tumors. Vascular endothelial growth factor (VEGF) is a major initiator and regulator of angiogenic processes and is associated with tumor growth, invasion and metastasis. The VEGF family of proteins (VEGF-A, VEGF-B, VEGF-C, VEGF-D and the placenta growth factor [PGF]) share tyrosine kinase receptors (VEGFR-1, VEGFR-2, **VEGFR-3**) which are expressed on many cell types including endothelial cells, hematopoietic stem cells and many solid tumor and leukemia blast cells. The **VEGF receptor** signaling pathway activates a tyrosine kinase cascade involving various intracellular proteins (particularly PI-3 and RAS/MAP kinases) and is a potential antiangiogenic target that can be inhibited at various levels. The work presented here deals primarily with the small molecule **tyrosine kinase inhibitors** such as adaphostin. Adaphostin and congeners have the potential to specifically inhibit tyrosine kinases of the **VEGF receptors** with an acceptable toxicity profile to the host. These compounds have shown good inhibition of VEGFR-1 and relatively good inhibition of VEGFR expressing human leukemia cells. Furthermore, combination regimens of this class of compounds with cytotoxic drugs can downregulate both angiogenesis and its associated effects in the bone marrow of mammalian systems and provide synergistic combination drug regimens for the treatment of refractory malignancies.

L47 ANSWER 6 OF 11 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003363878 EMBASE Angiogenesis in Cancer - International Meeting: 26-28 June 2003, Reykjavik, Iceland. Leenders W.. W. Leenders, University Medical Centre Nijmegen, 437 Department of Pathology, PO Box 9101, NL-6500 HB Nijmegen, Netherlands. w.leenders@pathol.umcn.nl. IDrugs 6/8 (743-745) 1 Aug 2003.
ISSN: 1369-7056. CODEN: IDRUFN. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The International Meeting

biological and molecular biological aspects of angiogenesis and lymphangiogenesis were highlighted, with special emphasis on VEGF-A (which is involved in angiogenesis), VEGF-C (which is involved in lymphangiogenesis) and the **VEGF receptors** VEGFR-1, VEGFR-2 and **VEGFR-3**. Detailed knowledge about these factors and the signaling cascades they induce has already revealed targets for intervention. Studies with molecules that target different phases of the process of blood vessel formation have been undertaken for many years and a number of them have proceeded into clinical trials. The development of small compound **tyrosine kinase inhibitors** is still ongoing, and preclinical and clinical data with some of these compounds were presented. The first trials carried out some years ago with anti-angiogenic compounds subdued the initial expectations for this approach as an anticancer therapy. This meeting allowed a renewed optimism to develop with the first presentation of data from the first successfully completed phase III trial with bevacizumab (Avastin; Genentech Inc/F Hoffmann-La Roche Ltd). However, it is also evident that patients enrolled in anti-angiogenic therapy trials must be carefully selected and criteria determined that are predictive of susceptibility to anti-angiogenic treatment.

L47 ANSWER 7 OF 11 MEDLINE on STN DUPLICATE 2

2003188024. PubMed ID: 12706123. Vascular endothelial growth factor (**VEGF**) **receptor**-2 signaling mediates VEGF-C(deltaNdeltaC)- and VEGF-A-induced angiogenesis in vitro. Tille Jean-Christophe; Wang Xueyan; Lipson Kenneth E; McMahon Gerald; Ferrara Napoleone; Zhu Zhenping; Hicklin Daniel J; Sleeman Jonathan P; Eriksson Ulf; Alitalo Kari; Pepper Michael S. (Department of Cell Biology and Morphology, University Medical Center, Geneva, Switzerland.) Experimental cell research, (2003 May 1) 285 (2) 286-98. Journal code: 0373226. ISSN: 0014-4827. Pub. country: United States. Language: English.

AB Angiogenesis and lymphangiogenesis are regulated by members of the vascular endothelial growth factor (VEGF) family of cytokines, which mediate their effects via tyrosine kinase **VEGF receptors** -1, -2, and -3. We have used wild-type and mutant forms of VEGFs -A, -B, and -C, a pan-VEGFR **tyrosine kinase inhibitor** (SU5416) as well as neutralizing anti-VEGFR-2 antibodies, to determine which **VEGF receptor**(s) are required for bovine endothelial cell invasion and tube formation in vitro. This was compared to the ability of these cytokines to induce expression of members of the plasminogen activator (PA)-plasmin system. We found that cytokines which bind VEGFR-2 (human VEGF-A, human VFM23A, human VEGF-C(deltaNdeltaC), and rat VEGF-C(152)) induced invasion, tube formation, urokinase-type-PA, tissue-type-PA, and PA inhibitor-1, invasion and tube formation as well as signaling via the MAP kinase pathway were efficiently blocked by SU5416 and anti-VEGFR-2 antibodies. In contrast, cytokines and mutants which exclusively bind VEGFR-1 (human VFM17 and human VEGF-B) had no effect on invasion and tube formation or on the regulation of gene expression. We were unable to identify cytokines which selectively stimulate bovine **VEGFR-3** in our system. Taken together, these findings point to the central role of VEGFR-2 in the angiogenic signaling pathways induced by VEGF-C(deltaNdeltaC) and VEGF-A.

L47 ANSWER 8 OF 11 MEDLINE on STN DUPLICATE 3

2002715982. PubMed ID: 12477352. Anthranilic acid amides: a novel class of antiangiogenic **VEGF receptor** kinase inhibitors. Manley

AB Two readily synthesized anthranilamide, **VEGF receptor tyrosine kinase inhibitors** have been prepared and evaluated as angiogenesis inhibitors. 2-[(4-Pyridyl)methyl]amino-N-[3-(trifluoromethyl)phenyl]benzamide (5) and N-3-isoquinolinyl-2-[(4-pyridinylmethyl)amino]benzamide (7) potently and selectively inhibit recombinant VEGFR-2 and **VEGFR-3** kinases. As a consequence of their physicochemical properties, these anthranilamides readily penetrate cells and are absorbed following once daily oral administration to mice. Both 5 and 7 potently inhibit VEGF-induced angiogenesis in an implant model, with ED(50) values of 7 mg/kg. In a mouse orthotopic model of melanoma, 5 and 7 potently inhibited both the growth of the primary tumor as well as the formation of spontaneous peripheral metastases. The anthranilamides 5 and 7 represent a new structural class of VEGFR kinase inhibitors, which possess potent antiangiogenic and antitumor properties.

L47 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN

2002:678706 Document No. 138:231379 The vascular endothelial growth factor receptor **tyrosine kinase inhibitor** PTK787/ZK222584 inhibits growth and migration of multiple myeloma cells in the bone marrow microenvironment. Lin, Boris; Podar, Klaus; Gupta, Deepak; Tai, Yu-Tzu; Li, Sigui; Weller, Edie; Hideshima, Teru; Lentzsch, Suzanne; Davies, Faith; Li, Cheng; Weisberg, Ellen; Schlossman, Robert L.; Richardson, Paul G.; Griffin, James D.; Wood, Jeanette; Munshi, Nikhil C.; Anderson, Kenneth C. (Jerome Lipper Multiple Myeloma Center, Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, MA, 02115, USA). Cancer Research, 62(17), 5019-5026 (English) 2002. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB Our prior studies show that multiple myeloma (MM) cell lines and patient cells express high-affinity vascular endothelial growth factor (**VEGF**) **receptor** (VEGFR) Flt-1 but not Flk-1/KDR. Moreover, these studies have shown that VEGF induces proliferation and migration of MM cells, and we have begun to delineate the signaling cascades mediating those sequelae. In this study, we examined the activity of PTK787/ZK 222584 (PTK787), a mol. designed to bind specifically to the tyrosine kinase domain of VEGFR and inhibit angiogenesis. We show that PTK787 acts both directly on MM cells and in the bone marrow microenvironment. Specifically, PTK787 (1-5 μM) inhibits proliferation of MM cells by 50%, as assayed by [3H]thymidine uptake. This effect of PTK787 is dose dependent in both MM cell lines and patient cells that are both sensitive and resistant to conventional therapy. PTK787 enhances the inhibitory effect of dexamethasone on growth of MM cells and can overcome the protective effect of interleukin 6 (IL-6) against dexamethasone-induced apoptosis. PTK787 (1 μM) also blocks VEGF-induced migration of MM cells across an extracellular matrix. Importantly, PTK787 also inhibits the increased MM cell proliferation and increased IL-6 and VEGF secretion in cultures of MM cells adherent to bone marrow stem cells. These findings therefore demonstrate that PTK787 both acts directly on MM cells and inhibits paracrine IL-6-mediated MM cell growth in the bone marrow milieu. The demonstrated anti-MM activity of PTK787, coupled with its antiangiogenic effects, provides the framework for clin. trials of this agent to overcome drug resistance and improve outcome in MM.

L47 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN

2002:549626 Document No. 138:147268 PTK787/ZK 222584, a specific vascular endothelial growth factor-receptor **tyrosine kinase inhibitor** affects the

4015-4022 (English) 2002. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB Antiangiogenic therapy is a promising new strategy of inhibiting tumor growth and formation of metastases. Recently, a number of compds. with different effects on tumor endothelial cells have entered clin. trials and revealed the need for diagnostic methods to detect their biol. activity. Dynamic enhanced magnetic resonance imaging (dyMRI) is used in most clin. trials with antiangiogenic active compds. We evaluated this method by using PTK787/ZK 222584, a specific inhibitor of the **VEGF-receptor** tyrosine kinases, which showed antitumoral and antiangiogenic activity in a murine renal cell carcinoma (RENCA) model. After intrarenal application of RENCA cells, mice developed a primary tumor and metastases to the lung and abdominal lymph nodes. After daily oral therapy for 21 days with either PTK787/ZK 222584 at a dose of 50 mg/kg or vehicle, primary tumors of all animals were analyzed by dyMRI. Gadolinium-DOTA (Dotarem) was used as a contrast agent to detect vessel permeability and contrast agent extravasation, whereas intravascular iron oxide nanoparticles (Endorem) were used to detect partial tumor blood volume Addnl., vessel d., architecture, diameter, and blood flow velocity were investigated by appropriate methods. Surprisingly, no changes in extravasation occurred under treatment with PTK787/ZK 222584 as compared with the control group, whereas a significant decrease in vessel permeability occurred. Furthermore, an increase in partial blood volume was found in the PTK787/ZK 222584-treated group, although vessel d. was reduced as seen by histol. Using the corrosion cast technique, reduction in vessel d. was significant but not very pronounced and predominantly attributable to the loss of microvessels only. This finding correlated with a shift to large vessel diams. in the primary tumors of PTK787/ZK 222584-treated animals and with reduction of blood flow velocity in the tumor feeding renal artery. From these findings, we conclude that the treatment with PTK787/ZK 222584 primarily reduces the number of tumor microvessels, accompanied by a hemodynamic dilation of the remaining vessels. This dilation could influence the result of dyMRI such that no change in extravasation or even an increase in partial tumor blood volume could be observed

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2001421508 EMBASE Vascular endothelial growth factor (**VEGF**) **receptor**-2 antagonists inhibit VEGF- and basic fibroblast growth factor-induced angiogenesis in vivo and in vitro. Tille J.-C.; Wood J.; Mandriota S.J.; Schnell C.; Ferrari S.; Mestan J.; Zhu Z.; Witte L.; Pepper M.S.. Dr. M.S. Pepper, Department of Morphology, University Medical Center, 1 Rue Michel Servet, 1211 Geneva 4, Switzerland. michael.pepper@medecine.unige.ch. Journal of Pharmacology and Experimental Therapeutics 299/3 (1073-1085) 2001.
Refs: 42.
ISSN: 0022-3565. CODEN: JPETAB. Pub. Country: United States. Language: English. Summary Language: English.

AB Exponential tumor growth is angiogenesis-dependent. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are potent angiogenic inducers that act synergistically in vivo and in vitro. We assessed the effect of specific inhibitors of **VEGF receptor** (VEGFR)-2 tyrosine kinase activity in in vivo and in vitro models of VEGF- and bFGF-induced angiogenesis. In an implant mouse model of angiogenesis, VEGFR-2 inhibitors completely blocked angiogenesis induced by VEGF, and surprisingly

BME and BAE cells produce VEGF and VEGF-C, which is not modulated by bFGF. Thus, the unexpected inhibition of bFGF-induced angiogenesis by VEGFR-2 antagonists reveals a requirement for endogenous VEGF and VEGF-C in this process. These findings broaden the spectrum of mediators of angiogenesis that can be inhibited by VEGFR-2 antagonists and highlight the importance of these compounds as agents for inhibiting tumor growth sustained by both VEGF and bFGF.

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